

**SEARCH REQUEST FORM**

Scientific and Technical Information Center

Requester's Full Name: \_\_\_\_\_ Examiner #: \_\_\_\_\_ Date: \_\_\_\_\_  
An Unit: \_\_\_\_\_ Phone Number 30 \_\_\_\_\_ Serial Number: \_\_\_\_\_  
Mail Box and Bldg/Room Location: \_\_\_\_\_ Results Format Preferred (circle): PAPER DISK E-MAIL

**if more than one search is submitted, please prioritize searches in order of need.**

\*\*\*\*\*

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: \_\_\_\_\_

Inventors (please provide full names): \_\_\_\_\_

Earliest Priority Filing Date: \_\_\_\_\_

*\* For Sequence Searches Only\* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

**STAFF USE ONLY**

Searcher: CE  
Searcher Phone #: 22504  
Searcher Location: \_\_\_\_\_  
Date Searcher Picked Up: 8/12  
Date Completed: 8/12  
Searcher Prep & Review Time: \_\_\_\_\_  
Clerical Prep Time: 15  
Online Time: 545

**Type of Search**

NA Sequence (#) \_\_\_\_\_  
AA Sequence (#) \_\_\_\_\_  
Structure (#) \_\_\_\_\_  
Bibliographic ☒  
Litigation \_\_\_\_\_  
Fulltext \_\_\_\_\_  
Patent Family \_\_\_\_\_  
Other \_\_\_\_\_

**Vendors and cost where applicable**

STN ☒  
Dialog \_\_\_\_\_  
Questel/Orbit \_\_\_\_\_  
Dr. Link \_\_\_\_\_  
Lexis/Nexis \_\_\_\_\_  
Sequence Systems \_\_\_\_\_  
WWW/Internet \_\_\_\_\_  
Other (specify) \_\_\_\_\_



# **STIC Search Report**

## **Biotech-Chem Library**

**STIC Database Tracking Number: 129646**

**TO: Emily M Le**  
**Location: 3c35 / 3c18**  
**Thursday, August 12, 2004**  
**Art Unit: 1648**  
**Phone: 272-0903**  
**Serial Number: 09 / 936449**

**From: Jan Delaval**  
**Location: Biotech-Chem Library**  
**Rem 1A51**  
**Phone: 272-2504**  
**jan.delaval@uspto.gov**

### **Search Notes**

129646

Delaval, Jan

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**From:** Le, Emily  
**Sent:** Wednesday, August 11, 2004 10:24 AM  
**To:** Delaval, Jan  
**Subject:** STN search: 09/936449

Jan,

Please provide a search for the following concept:

1. coumarin and chaperone
2. coumarin and chaperone and heat shock

synonyms:

coumarin: novobiocin, chlorobiocin, \$hydroxycoumarin, dicumarol, warfarin, phenprocoumon, coumermycin

chaperone: chaperonin, heat shock protein (particularly heat shock protein 90, also known as Hsp90).

priority date: 03/12/1999

inventors: [http://expoweb1:8001/cgi-bin/expo/GenInfo/sninventors.pl?APPL\\_ID=09936449](http://expoweb1:8001/cgi-bin/expo/GenInfo/sninventors.pl?APPL_ID=09936449)

Thanks, Jan!

Emily Le  
Remsen, 3C35  
(571) 272-0903

=> d his

(FILE 'HOME' ENTERED AT 09:01:18 ON 12 AUG 2004)  
SET COST OFF

FILE 'REGISTRY' ENTERED AT 09:01:33 ON 12 AUG 2004

E COUMARIN/CN  
L1 1 S E3  
E NOVOBIOCIN/CN  
L2 1 S E3  
E CHLOROBIOCIN/CN  
L3 1 S E3  
E HYDROXYCOUMARIN/CN  
L4 1 S E3  
E DICUMAROL/CN  
L5 1 S E3  
E WARFARIN/CN  
L6 1 S E3  
E PHENPROCOUMON/CN  
L7 1 S E3  
E COUMERMYCIN/CN  
L8 1 S E3  
L9 8 S L1-L8  
SEL RN  
L10 213 S E1-E8/CRN  
L11 130 S L10 NOT (PMS OR IDS OR MXS OR MNS)/CI  
L12 21 S L11 NOT (COMP D OR WITH OR UNSPECIFIED OR CONJUGATE)  
L13 192 S L10 NOT L12  
L14 10774 S COUMARIN OR NOVOBIOCIN OR CHLOROBIOCIN OR HYDROXYCOUMARIN OR  
L15 10680 S L14 NOT L9,L10

FILE 'HCAPLUS' ENTERED AT 09:05:11 ON 12 AUG 2004

L16 14477 S L9 OR L12  
L17 219 S L13  
L18 33774 S L15  
L19 42695 S ?COUMARIN? OR ?NOVOBIOCIN? OR ?CHLOROBIOCIN? OR ?HYDROXYCOUMA  
L20 1187 S COUMADIN? OR 2H 1 BENZOPYRAN 2 ONE  
L21 1146 S DICOUMAROL  
L22 57132 S L16-L21  
E HEAT SHOCK PROTEIN/CT  
L23 21562 S HEAT SHOCK(L) PROTEIN  
E HEAT-SHOCK/CT  
L24 1699 S E62-E65  
L25 9914 S E32-E61,E66-E68  
E E32+ALL  
L26 15973 S E3-E6,E2+NT  
E HSP90  
L27 2401 S E3-E19  
L28 5 S E34  
L29 3101 S HSP90 OR HSP 90  
E CHAPERONE/CT  
E E4+ALL  
E E2+ALL  
L30 6435 S E3,E4,E2+NT  
E CHAPERONIN/CT  
L31 2560 S E6-E12  
E E6+ALL  
L32 11816 S CHAPERON?  
L33 90 S L22 AND L23-L32  
L34 51 S L33 AND (PD<=19990312 OR PRD<=19990312 OR AD<=19990312)  
E MARCU M/AU  
L35 65 S E3,E4,E16,E17  
E MECKERS L/AU

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          E NECKERS L/AU
L36      220 S E3-E8
          E SCHULTE T/AU
L37      37 S E3,E7,E9-E13
L38      4 S L33 AND L35-L37
L39      1 S L34 AND L38
L40      4 S L38,L39
L41      50 S L34 NOT L40
L42      7 S L41 AND (PHARMACEUT? OR PHARMACOL?)/SC,SX
          SEL DN AN 2 5 6 7 L42
L43      4 S L42 AND E1-E12
L44      43 S L41 NOT L42
          SEL DN AN L44 5 19 30 33 36 37 43
L45      7 S L44 AND E13-E33
L46      15 S L40,L43,L45 AND L16-L45
L47      15 S L46 AND (HSP? OR HEAT SHOCK OR ?PROTEIN? OR 90)
L48      3 S L47 AND ?CHAPERON?
L49      15 S L47,L48
          SEL HIT RN

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FILE 'REGISTRY' ENTERED AT 09:23:40 ON 12 AUG 2004

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L50      7 S E34-E40
L51      3 S L50 AND L9,L12
L52      4 S L50 AND L13,L15
L53      12 S L9,L50-L52

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=> fil reg

FILE 'REGISTRY' ENTERED AT 09:24:39 ON 12 AUG 2004

USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.

PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

COPYRIGHT (C) 2004 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 11 AUG 2004 HIGHEST RN 725685-10-9

DICTIONARY FILE UPDATES: 11 AUG 2004 HIGHEST RN 725685-10-9

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:

<http://www.cas.org/ONLINE/DBSS/registryss.html>

=> d ide can tot l53

L53 ANSWER 1 OF 12 REGISTRY COPYRIGHT 2004 ACS on STN

RN 78040-85-4 REGISTRY

CN Coumermycin (7CI, 9CI) (CA INDEX NAME)

MF Unspecified

CI MAN

LC STN Files: AGRICOLA, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAOLD, CAPLUS, EMBASE, IPA, NAPRALERT, PHAR, TOXCENTER, USPATFULL

DT.CA Cplus document type: Conference; Journal; Patent

RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); PROC (Process); USES (Uses)

RLD.P Roles for non-specific derivatives from patents: BIOL (Biological

study); USES (Uses)

RL.NP Roles from non-patents: BIOL (Biological study); PROC (Process); PRP (Properties); USES (Uses)

\*\*\* STRUCTURE DIAGRAM IS NOT AVAILABLE \*\*\*

69 REFERENCES IN FILE CA (1907 TO DATE)

1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

69 REFERENCES IN FILE CAPLUS (1907 TO DATE)

1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 141:82297

REFERENCE 2: 140:105321

REFERENCE 3: 140:88377

REFERENCE 4: 139:194893

REFERENCE 5: 136:259921

REFERENCE 6: 136:98820

REFERENCE 7: 136:689

REFERENCE 8: 135:339201

REFERENCE 9: 135:133932

REFERENCE 10: 135:51028

L53 ANSWER 2 OF 12 REGISTRY COPYRIGHT 2004 ACS on STN

RN 51050-59-0 REGISTRY

CN 1H-2-Benzopyran-1-one, 3,4-dichloro- (9CI) (CA INDEX NAME)

OTHER NAMES:

CN 3,4-Dichloroisocoumarin

FS 3D CONCORD

MF C9 H4 Cl2 O2

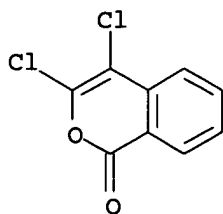
LC STN Files: AGRICOLA, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CHEMCATS, CIN, CSCHEM, DDFU, DRUGU, EMBASE, MEDLINE, MSDS-OHS, TOXCENTER, USPAT2, USPATFULL

DT.CA Caplus document type: Conference; Journal; Patent

RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses)

RLD.NP Roles for non-specific derivatives from non-patents: BIOL (Biological study)



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

84 REFERENCES IN FILE CA (1907 TO DATE)  
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA  
84 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:402221  
REFERENCE 2: 140:389052  
REFERENCE 3: 140:315899  
REFERENCE 4: 140:175176  
REFERENCE 5: 140:157485  
REFERENCE 6: 140:82342  
REFERENCE 7: 140:38536  
REFERENCE 8: 139:318425  
REFERENCE 9: 139:288166  
REFERENCE 10: 139:129917

L53 ANSWER 3 OF 12 REGISTRY COPYRIGHT 2004 ACS on STN

RN 43070-85-5 REGISTRY

CN 2H-1-Benzopyran-2-one, hydroxy- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Coumarin, hydroxy- (7CI)

OTHER NAMES:

CN Hydroxy-2H-1-benzopyran-2-one

CN **Hydroxycoumarin**

CN Oxycoumarin

MF C9 H6 O3

CI IDS

LC STN Files: AGRICOLA, AQUIRE, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAOLD, CAPLUS, EMBASE, NAPRALERT, TOXCENTER, USPAT2, USPATFULL

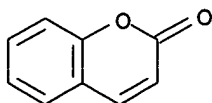
DT.CA Caplus document type: Conference; Journal; Patent

RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

RLD.P Roles for non-specific derivatives from patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

RL.NP Roles from non-patents: BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)

RLD.NP Roles for non-specific derivatives from non-patents: BIOL (Biological study); OCCU (Occurrence); PROC (Process); USES (Uses)



D1-OH

62 REFERENCES IN FILE CA (1907 TO DATE)  
25 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA  
63 REFERENCES IN FILE CAPLUS (1907 TO DATE)  
1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 141:11954  
REFERENCE 2: 140:368059  
REFERENCE 3: 140:292209  
REFERENCE 4: 140:154111  
REFERENCE 5: 140:154092  
REFERENCE 6: 140:89776  
REFERENCE 7: 139:360902  
REFERENCE 8: 139:311934  
REFERENCE 9: 139:280895  
REFERENCE 10: 139:280893

L53 ANSWER 4 OF 12 REGISTRY COPYRIGHT 2004 ACS on STN

RN 39868-96-7 REGISTRY

CN Benzamide, N-[8-chloro-7-[[6-deoxy-5-C-methyl-4-O-methyl-3-O-[(5-methyl-1H-pyrrol-2-yl)carbonyl]- $\alpha$ -L-lyxo-hexopyranosyl]oxy]-4-hydroxy-2-oxo-2H-1-benzopyran-3-yl]-4-hydroxy-3-(3-methyl-2-butenyl)- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN 1H-Pyrrole-2-carboxylic acid, 5-methyl-, 3'-ester with  
N-[8-chloro-7-[[6-deoxy-5-C-methyl-4-O-methyl- $\alpha$ -L-lyxo-hexopyranosyl]oxy]-4-hydroxy-2-oxo-2H-1-benzopyran-3-yl]-4-hydroxy-3-(3-methyl-2-butenyl)benzamide

OTHER NAMES:

CN 18631RP

CN Antibiotic 2562A

CN Chlorobiocin

CN Clorobiocin

CN NSC 227186

CN RP 18631

FS STEREOSEARCH

DR 9037-72-3, 36631-40-0, 69343-32-4, 26637-98-9, 34628-96-1

MF C35 H37 Cl N2 O11

CI COM

LC STN Files: BEILSTEIN\*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, RTECS\*, TOXCENTER, USPATFULL

(\*File contains numerically searchable property data)

DT.CA Caplus document type: Journal; Patent

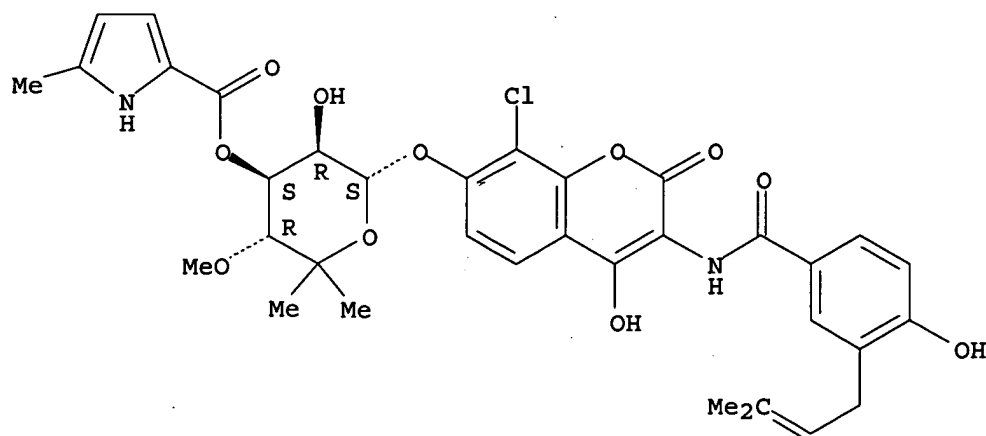
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

RL.NP Roles from non-patents: BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

RLD.NP Roles for non-specific derivatives from non-patents: BIOL (Biological study); PROC (Process); PRP (Properties)

Absolute stereochemistry.





\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

49 REFERENCES IN FILE CA (1907 TO DATE)  
 3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA  
 52 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:265188  
 REFERENCE 2: 140:159453  
 REFERENCE 3: 140:76987  
 REFERENCE 4: 140:58478  
 REFERENCE 5: 139:377683  
 REFERENCE 6: 139:303700  
 REFERENCE 7: 139:64106  
 REFERENCE 8: 139:18887  
 REFERENCE 9: 138:182118  
 REFERENCE 10: 137:87839

L53 ANSWER 5 OF 12 REGISTRY COPYRIGHT 2004 ACS on STN

RN 4434-05-3 REGISTRY

CN 1H-Pyrrole-2,4-dicarboxamide, N,N'-bis[7-[[6-deoxy-5-C-methyl-4-O-methyl-3-O-[(5-methyl-1H-pyrrol-2-yl)carbonyl]-α-L-lyxo-hexopyranosyl]oxy]-4-hydroxy-8-methyl-2-oxo-2H-1-benzopyran-3-yl]-3-methyl- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN 1H-Pyrrole-2-carboxylic acid, 5-methyl-, diester with N,N'-bis[7-[[6-deoxy-5-C-methyl-4-O-methyl-α-L-lyxo-hexopyranosyl]oxy]-4-hydroxy-8-methyl-2-oxo-2H-1-benzopyran-3-yl]-3-methyl-1H-pyrrole-2,4-dicarboxamide

CN Coumarin, 3,3'-[(3-methylpyrrole-2,4-diyl)bis(carbonylimino)]bis[7-[(5,5-di-C-methyl-4-O-methyl-α-L-lyxopyranosyl)oxy]-4-hydroxy-8-methyl-, bis(5-methylpyrrole-2-carboxylate) (ester) (8CI)

CN Coumerymycin A1 (7CI)

CN Pyrrole-2-carboxylic acid, 5-methyl-, diester with 3,3'-[(3-methylpyrrole-2,4-diyl)bis(carbonylimino)]bis[7-[(5,5-di-C-methyl-4-O-methyl-α-L-lyxopyranosyl)oxy]-4-hydroxy-8-methylcoumarin] (8CI)

## OTHER NAMES:

CN Coumamycin  
 CN Notomycin A1  
 CN NSC 107412  
 FS STEREOSEARCH  
 DR 11035-12-4, 1372-92-5, 22260-48-6, 22850-02-8, 23249-07-2, 30418-37-2,  
 30546-09-9  
 MF C55 H59 N5 O20  
 CI COM  
 LC STN Files: AGRICOLA, ANABSTR, BEILSTEIN\*, BIOBUSINESS, BIOSIS,  
 BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CHEMCATS,  
 CSCHEM, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IMSDRUGNEWS,  
 IMSRESEARCH, IPA, MEDLINE, MSDS-OHS, PHAR, RTECS\*, TOXCENTER, USAN,  
 USPAT2, USPATFULL

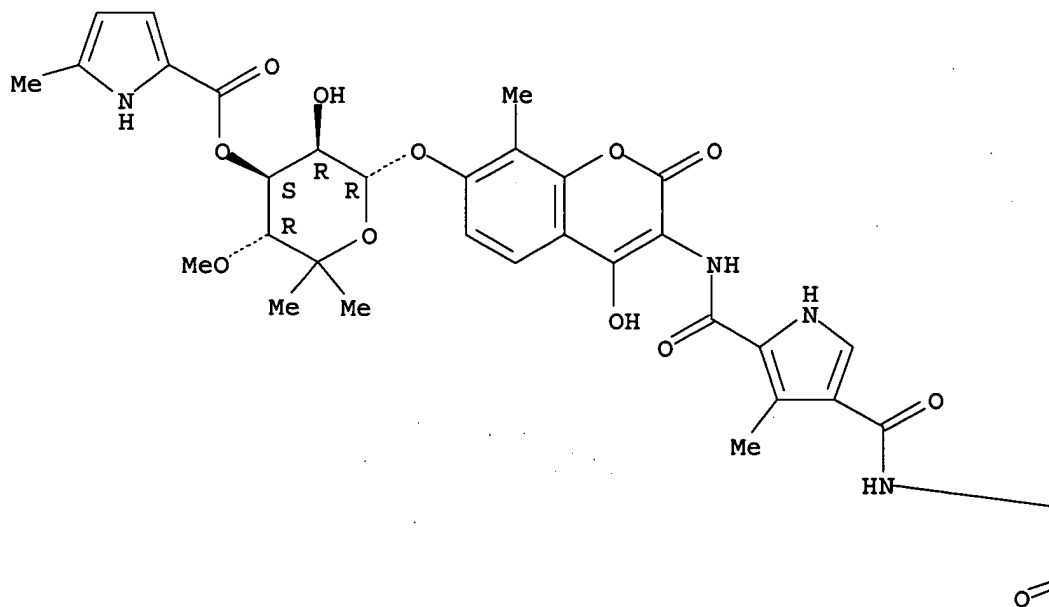
(\*File contains numerically searchable property data)

Other Sources: WHO

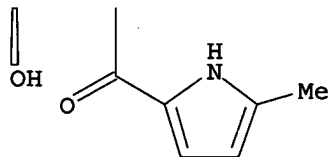
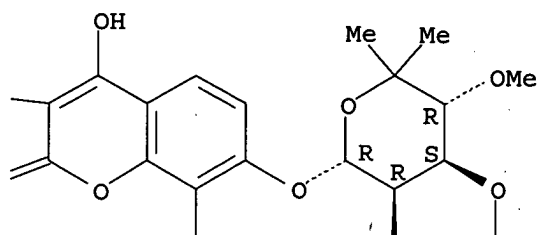
DT.CA Caplus document type: Conference; Dissertation; Journal; Patent  
 RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); PROC  
 (Process); USES (Uses); NORL (No role in record)  
 RLD.P Roles for non-specific derivatives from patents: BIOL (Biological  
 study)  
 RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological  
 study); FORM (Formation, nonpreparative); PREP (Preparation); PROC  
 (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses);  
 NORL (No role in record)  
 RLD.NP Roles for non-specific derivatives from non-patents: BIOL (Biological  
 study); PREP (Preparation); PRP (Properties)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



PAGE 2-B

\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

202 REFERENCES IN FILE CA (1907 TO DATE)  
3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA  
202 REFERENCES IN FILE CAPLUS (1907 TO DATE)  
7 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 140:265188  
REFERENCE 2: 140:123415  
REFERENCE 3: 139:242267  
REFERENCE 4: 139:240318  
REFERENCE 5: 139:97752  
REFERENCE 6: 139:64106  
REFERENCE 7: 138:354143  
REFERENCE 8: 138:332654

REFERENCE 9: 138:270349

REFERENCE 10: 138:182118

L53 ANSWER 6 OF 12 REGISTRY COPYRIGHT 2004 ACS on STN

RN 435-97-2 REGISTRY

CN 2H-1-Benzopyran-2-one, 4-hydroxy-3-(1-phenylpropyl)- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Coumarin, 3-( $\alpha$ -ethylbenzyl)-4-hydroxy- (8CI)

OTHER NAMES:

CN ( $\pm$ )-Phenprocoumon

CN 3-( $\alpha$ -Ethylbenzyl)-4-hydroxycoumarin

CN 3-( $\alpha$ -Phenylpropyl)-4-hydroxycoumarin

CN 3-(1-Phenylpropyl)-4-hydroxycoumarin

CN 4-Hydroxy-2-oxo-3-(1-phenylpropyl)-2H-chromene

CN DL-3-( $\alpha$ -Ethylbenzyl)-4-hydroxycoumarin

CN Falithrom

CN Fencumar

CN Liquamar

CN Marcoumar

CN Marcumar

CN Phenprocoumarol

CN Phenprocoumarole

CN **Phenprocoumon**

CN Ro 1-4849

FS 3D CONCORD

DR 5999-41-7

MF C18 H16 O3

CI COM

LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN\*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, DDFU, DIOGENES, DRUGU, EMBASE, HSDB\*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK\*, MSDS-OHS, NIOSHTIC, PS, RTECS\*, SPECINFO, TOXCENTER, USAN, USPAT2, USPATFULL

(\*File contains numerically searchable property data)

Other Sources: EINECS\*\*, WHO

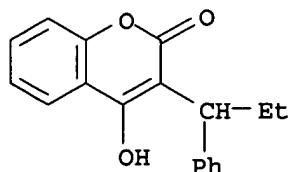
(\*\*Enter CHEMLIST File for up-to-date regulatory information)

DT.CA Caplus document type: Conference; Dissertation; Journal; Patent; Report

RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses); NORL (No role in record)

RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)

RLD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

448 REFERENCES IN FILE CA (1907 TO DATE)

3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

449 REFERENCES IN FILE CAPLUS (1907 TO DATE)

8 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 141:64421  
REFERENCE 2: 141:17265  
REFERENCE 3: 141:16830  
REFERENCE 4: 141:16692  
REFERENCE 5: 140:228933  
REFERENCE 6: 140:191764  
REFERENCE 7: 140:174382  
REFERENCE 8: 140:174256  
REFERENCE 9: 140:139020  
REFERENCE 10: 140:12770

L53 ANSWER 7 OF 12 REGISTRY COPYRIGHT 2004 ACS on STN

RN 303-81-1 REGISTRY

CN Benzamide, N-[7-[[3-O-(aminocarbonyl)-6-deoxy-5-C-methyl-4-O-methyl- $\alpha$ -L-lyxo-hexopyranosyl]oxy]-4-hydroxy-8-methyl-2-oxo-2H-1-benzopyran-3-yl]-4-hydroxy-3-(3-methyl-2-butenyl)- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Coumarin, 7-[4-(carbamoyloxy)tetrahydro-3-hydroxy-5-methoxy-6,6-dimethylpyran-2-yloxy]-4-hydroxy-3-[4-hydroxy-3-(3-methyl-2-butenyl)benzamido]-8-methyl- (6CI)

CN Novobiocin (8CI)

OTHER NAMES:

CN Albamix

CN Albamycin

CN Antibiotic PA-93

CN Cardelmycin

CN Cathocin

CN Cathomycin

CN Crystallinic acid

CN Inamycin

CN Novo-R

CN PA 93

CN Robiocina

CN Sirbiocina

CN Spheromycin

CN Stilbiocina

CN Streptonivicin

CN U 6391

FS STEREOSEARCH

DR 8028-29-3, 107781-69-1

MF C31 H36 N2 O11

CI COM

LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN\*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN, DDFU, DIOGENES, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK\*, NAPRALERT, NIOSHTIC, PROMT, PS, RTECS\*, TOXCENTER, USAN, USPAT2, USPATFULL, VETU

(\*File contains numerically searchable property data)

Other Sources: EINECS\*\*, WHO

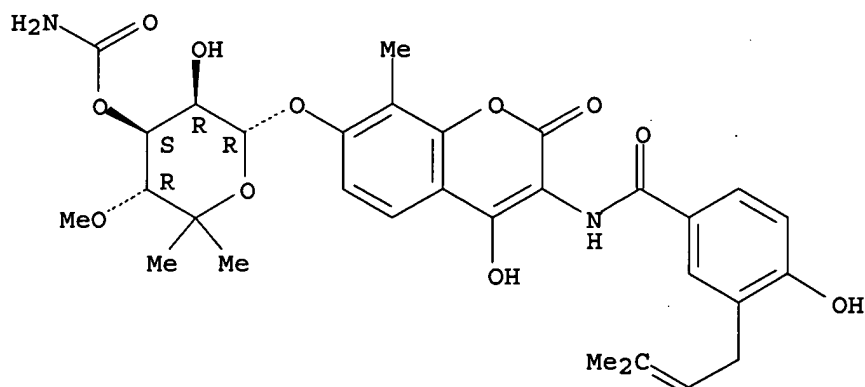
(\*\*Enter CHEMLIST File for up-to-date regulatory information)

DT.CA Caplus document type: Book; Conference; Dissertation; Journal; Patent; Report

RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study);

PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)  
 RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); USES (Uses)  
 RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)  
 RLD.NP Roles for non-specific derivatives from non-patents: BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties)

Absolute stereochemistry.



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

1915 REFERENCES IN FILE CA (1907 TO DATE)  
 11 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA  
 1923 REFERENCES IN FILE CAPLUS (1907 TO DATE)  
 80 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 141:111566  
 REFERENCE 2: 141:88025  
 REFERENCE 3: 141:82294  
 REFERENCE 4: 141:68099  
 REFERENCE 5: 141:20357  
 REFERENCE 6: 141:4024  
 REFERENCE 7: 141:4020  
 REFERENCE 8: 141:3658  
 REFERENCE 9: 140:420526  
 REFERENCE 10: 140:388532

L53 ANSWER 8 OF 12 REGISTRY COPYRIGHT 2004 ACS on STN  
 RN 298-81-7 REGISTRY  
 CN 7H-Furo[3,2-g][1]benzopyran-7-one, 9-methoxy- (8CI, 9CI) (CA INDEX NAME)  
 OTHER CA INDEX NAMES:

CN 5-Benzofuranacrylic acid, 6-hydroxy-7-methoxy-, 8-lactone (7CI)

OTHER NAMES:

CN 8-Methoxy-6,7-furanocoumarin  
 CN 8-Methoxypsoralen  
 CN 8-Methoxypsoralene  
 CN 8-Methoxy[furano-3',2':6,7-coumarin]  
 CN 8-MOP  
 CN 8-MP  
 CN Ammodin  
 CN Ammoidin  
 CN Deltapsoralen  
 CN Geroxalen  
 CN Meladinin  
 CN Meladinine  
 CN Meladoxen  
 CN Meloxine  
 CN Methoxa-Dome  
 CN Methoxsalen  
 CN New-Meladinin  
 CN NSC 45923  
 CN Oxsoralen  
 CN Oxsoralen Lotion  
 CN Oxsoralen-Ultra  
 CN Oxypsoralen  
 CN Puvalen  
 CN Puvamet  
 CN Uvadex  
 CN Xanthotoxin  
 CN Xanthotoxine  
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 CI COM

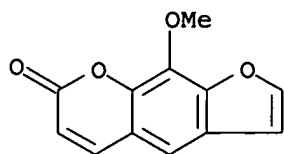
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN\*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSChem, CSNB, DDFU, DIOGENES, DRUGU, EMBASE, HODOC\*, HSDB\*, IFICDB, IFIPAT, IFIUDb, IMSCoSEARCH, IPA, MEDLINE, MRCK\*, NAPRALERT, NIOSHTIC, PIRA, PROMT, PS, RTECS\*, SPECINFO, TOXCENTER, USAN, USPAT2, USPATFULL

(\*File contains numerically searchable property data)

Other Sources: DSL\*\*, EINECS\*\*, TSCA\*\*

(\*\*Enter CHEMLIST File for up-to-date regulatory information)

DT.CA Caplus document type: Conference; Dissertation; Journal; Patent; Report  
 RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)  
 RLD.P Roles for non-specific derivatives from patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)  
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 RLD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

2979 REFERENCES IN FILE CA (1907 TO DATE)  
 99 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA  
 2984 REFERENCES IN FILE CAPLUS (1907 TO DATE)  
 1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 141:105262  
 REFERENCE 2: 141:98979  
 REFERENCE 3: 141:84016  
 REFERENCE 4: 141:68239  
 REFERENCE 5: 141:66689  
 REFERENCE 6: 141:49976  
 REFERENCE 7: 141:49677  
 REFERENCE 8: 141:36293  
 REFERENCE 9: 141:35573  
 REFERENCE 10: 141:35559

L53 ANSWER 9 OF 12 REGISTRY COPYRIGHT 2004 ACS on STN

RN 91-64-5 REGISTRY

CN 2H-1-Benzopyran-2-one (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Coumarin (8CI)

OTHER NAMES:

CN 1,2-Benzopyrone

CN 2-Propenoic acid, 3-(2-hydroxyphenyl)-,  $\delta$ -lactone

CN 5,6-Benzo-2-pyrone

CN Benzo- $\alpha$ -pyrone

CN cis-o-Coumarinic acid lactone

CN Coumarinic anhydride

CN NSC 8774

CN o-Hydroxycinnamic acid lactone

CN Rattex

CN Tonka bean camphor

FS 3D CONCORD

MF C9 H6 O2

CI COM

LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN\*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHM, CSNB, DDFU, DETHERM\*, DIOGENES, DRUGU, EMBASE, GMELIN\*, HODOC\*, HSDB\*, IFICDB, IFIPAT, IFIADB, IPA, MEDLINE, MRCK\*, MSDS-OHS, NAPRALERT, NIOSHTIC, PDLCOM\*, PIRA, PROMT, RTECS\*, SPECINFO, TOXCENTER, ULIDAT, USAN, USPAT2, USPATFULL



(\*File contains numerically searchable property data)

Other Sources: DSL\*\*, EINECS\*\*, TSCA\*\*

(\*\*Enter CHEMLIST File for up-to-date regulatory information)

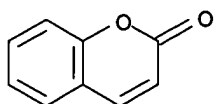
DT.CA Caplus document type: Book; Conference; Dissertation; Journal; Patent; Report

RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)

RLD.P Roles for non-specific derivatives from patents: ANST (Analytical study); BIOL (Biological study); CMBI (Combinatorial study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)

RLD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical study); BIOL (Biological study); CMBI (Combinatorial study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

7095 REFERENCES IN FILE CA (1907 TO DATE)  
 1536 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA  
 7108 REFERENCES IN FILE CAPLUS (1907 TO DATE)  
 10 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 141:103353

REFERENCE 2: 141:103129

REFERENCE 3: 141:98979

REFERENCE 4: 141:94452

REFERENCE 5: 141:94403

REFERENCE 6: 141:93467

REFERENCE 7: 141:90917

REFERENCE 8: 141:88915

REFERENCE 9: 141:81675

REFERENCE 10: 141:73658

L53 ANSWER 10 OF 12 REGISTRY COPYRIGHT 2004 ACS on STN

RN 81-81-2 REGISTRY

CN 2H-1-Benzopyran-2-one, 4-hydroxy-3-(3-oxo-1-phenylbutyl)- (9CI) (CA INDEX NAME)

## OTHER CA INDEX NAMES:

CN Coumarin, 3-( $\alpha$ -acetonylbenzyl)-4-hydroxy- (7CI, 8CI)

## OTHER NAMES:

CN ( $\pm$ )-WarfarinCN ( $\pm$ )-Warfarin-alcohol

CN (RS)-Warfarin

CN 1-(4'-Hydroxy-3'-coumarinyl)-1-phenyl-3-butanone

CN 3-( $\alpha$ -Acetonylbenzyl)-4-hydroxycoumarinCN 3-( $\alpha$ -Phenyl- $\beta$ -acetylethyl)-4-hydroxycoumarin

CN 3-(1'-Phenyl-2'-acetylethyl)-4-hydroxycoumarin

CN 4-Hydroxy-3-(3-oxo-1-phenylbutyl)-2H-chromen-2-one

CN Athrombine-K

CN Brumolin

CN Co-Rax

CN Compound 42

CN Coumafen

CN Coumafene

CN Coumaphen

CN Coumefene

CN Dethmor

CN DL-3-( $\alpha$ -Acetonylbenzyl)-4-hydroxycoumarin

CN Kumader

CN Kumadu

CN Kumatox

CN NSC 59813

CN rac-Warfarin

CN Ratron

CN Ratron G

CN Rodafarin

CN Rodafarin C

CN Rodex

CN Temus W

CN Vampirinip II

CN Vampirinip III

CN W.A.R.F. 42

CN WARF compound 42

CN **Warfarin**

CN Zoocoumarin

FS 3D CONCORD

DR 56573-89-8, 5543-56-6

MF C19 H16 O4

CI COM

LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN\*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CHEMSAFE, CIN, CSCHM, CSNB, DIOGENES, EMBASE, HODOC\*, HSDB\*, IFICDB, IFIPAT, IFIUDB, IMSCOSEARCH, IPA, MEDLINE, MRCK\*, MSDS-OHS, NIOSHTIC, PIRA, PROMT, PS, RTECS\*, SPECINFO, TOXCENTER, ULIDAT, USAN, USPAT2, USPATFULL

(\*File contains numerically searchable property data)

Other Sources: DSL\*\*, EINECS\*\*, TSCA\*\*, WHO

(\*\*Enter CHEMLIST File for up-to-date regulatory information)

DT.CA Caplus document type: Book; Conference; Dissertation; Journal; Patent; Report

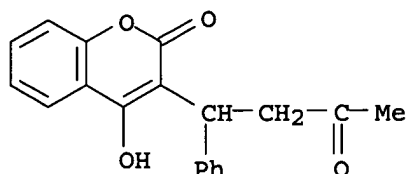
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)

RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); PREP (Preparation); PRP (Properties); USES (Uses)

RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)

RLD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical

study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses)



**\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\***

3455 REFERENCES IN FILE CA (1907 TO DATE)  
 49 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA  
 3466 REFERENCES IN FILE CAPLUS (1907 TO DATE)  
 1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 141:101526  
 REFERENCE 2: 141:99392  
 REFERENCE 3: 141:94452  
 REFERENCE 4: 141:81658  
 REFERENCE 5: 141:81573  
 REFERENCE 6: 141:81562  
 REFERENCE 7: 141:81362  
 REFERENCE 8: 141:76895  
 REFERENCE 9: 141:69470  
 REFERENCE 10: 141:64757

L53 ANSWER 11 OF 12 REGISTRY COPYRIGHT 2004 ACS on STN

RN 66-97-7 REGISTRY

CN 7H-Furo[3,2-g][1]benzopyran-7-one (8CI, 9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Furocoumarin (6CI)

OTHER NAMES:

CN 2-Propenoic acid, 3-(6-hydroxy-5-benzofuranyl)-, 8-lactone

CN 6,7-Furanocoumarin

CN Ficusin

CN Furo[2',3':7,6]coumarin

CN Furo[4',5':6,7]coumarin

CN NSC 404562

CN Psoralen

CN Psoralene

FS 3D CONCORD

MF C11 H6 O3

CI COM

LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN\*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU, EMBASE, HSDB\*, IFICDB,

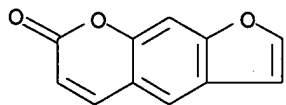
IFIPAT, IFIUDB, IPA, MEDLINE, MRCK\*, NAPRALERT, NIOSHTIC, PROMT, RTECS\*,  
SPECINFO, TOXCENTER, USPAT2, USPATFULL

(\*File contains numerically searchable property data)

Other Sources: EINECS\*\*

(\*\*Enter CHEMLIST File for up-to-date regulatory information)

DT.CA Caplus document type: Book; Conference; Dissertation; Journal; Patent;  
Report  
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study);  
OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties);  
RACT (Reactant or reagent); USES (Uses); NORL (No role in record)  
RLD.P Roles for non-specific derivatives from patents: ANST (Analytical  
study); BIOL (Biological study); PREP (Preparation); PROC (Process);  
RACT (Reactant or reagent); USES (Uses)  
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological  
study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP  
(Preparation); PROC (Process); PRP (Properties); RACT (Reactant or  
reagent); USES (Uses); NORL (No role in record)  
RLD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical  
study); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU  
(Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT  
(Reactant or reagent); USES (Uses)



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

2034 REFERENCES IN FILE CA (1907 TO DATE)  
598 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA  
2036 REFERENCES IN FILE CAPLUS (1907 TO DATE)  
31 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 141:105262  
REFERENCE 2: 141:85492  
REFERENCE 3: 141:84727  
REFERENCE 4: 141:50444  
REFERENCE 5: 141:49162  
REFERENCE 6: 141:36293  
REFERENCE 7: 141:22217  
REFERENCE 8: 141:19881  
REFERENCE 9: 141:18849  
REFERENCE 10: 141:18689

L53 ANSWER 12 OF 12 REGISTRY COPYRIGHT 2004 ACS on STN

RN 66-76-2 REGISTRY

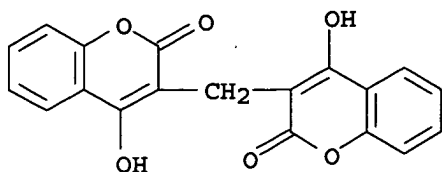
CN 2H-1-Benzopyran-2-one, 3,3'-methylenebis[4-hydroxy- (9CI) (CA INDEX NAME)

OTHER CA INDEX NAMES:

CN Coumarin, 3,3'-methylenebis[4-hydroxy- (8CI)

OTHER NAMES:

CN 3,3'-Methylenebis[4-hydroxy-1,2-benzopyrone]  
 CN 3,3'-Methylenebis[4-hydroxycoumarin]  
 CN Acadyl  
 CN Acavyl  
 CN Antitrombosin  
 CN Baracoumin  
 CN Bis(4-hydroxycoumarin-3-yl)methane  
 CN Bis-3,3'-(4-hydroxycoumarinyl)methane  
 CN Bishydroxycoumarin  
 CN Cuma  
 CN Cumid  
 CN Di-4-hydroxy-3,3'-methylenedicoumarin  
 CN Dicoumal  
 CN Dicoumarin  
 CN Dicoumarol  
 CN Dicuman  
 CN Dicumarine  
 CN **Dicumarol**  
 CN Dicumol  
 CN Dufalone  
 CN Kumoran  
 CN Melitoxin  
 CN NC 034  
 CN NSC 17860  
 CN NSC 221570  
 CN NSC 41834  
 CN Temparin  
 CN Trombosan  
 FS 3D CONCORD  
 MF C19 H12 O6  
 CI COM  
 LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN\*, BIOBUSINESS,  
 BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CEN,  
 CHEMCATS, CHEMINFORMRX, CHEMLIST, CSCHM, CSNB, DDFU, DIOGENES, DRUGU,  
 EMBASE, HODOC\*, HSDB\*, IFICDB, IFIUDB, IPA, MEDLINE, MRCK\*, MSDS-OHS,  
 NIOSHTIC, PROMT, RTECS\*, SPECINFO, TOXCENTER, USAN, USPAT2, USPATFULL  
 (\*File contains numerically searchable property data)  
 Other Sources: EINECS\*\*, NDSL\*\*, TSCA\*\*, WHO  
 (\*\*Enter CHEMLIST File for up-to-date regulatory information)  
 DT.CA Caplus document type: Book; Conference; Dissertation; Journal; Patent;  
 Report  
 RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study);  
 FORM (Formation, nonpreparative); PROC (Process); PRP (Properties); RACT  
 (Reactant or reagent); USES (Uses); NORL (No role in record)  
 RLD.P Roles for non-specific derivatives from patents: BIOL (Biological  
 study); PREP (Preparation); USES (Uses)  
 RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological  
 study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU  
 (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT  
 (Reactant or reagent); USES (Uses); NORL (No role in record)  
 RLD.NP Roles for non-specific derivatives from non-patents: BIOL (Biological  
 study); FORM (Formation, nonpreparative); PREP (Preparation); PRP  
 (Properties); USES (Uses)



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

1552 REFERENCES IN FILE CA (1907 TO DATE)  
20 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA  
1553 REFERENCES IN FILE CAPLUS (1907 TO DATE)  
26 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 141:33315  
REFERENCE 2: 141:2997  
REFERENCE 3: 140:394622  
REFERENCE 4: 140:316401  
REFERENCE 5: 140:297538  
REFERENCE 6: 140:228342  
REFERENCE 7: 140:169447  
REFERENCE 8: 140:169387  
REFERENCE 9: 140:90438  
REFERENCE 10: 140:87232

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FILE 'HCAPLUS' ENTERED AT 09:24:50 ON 12 AUG 2004

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FILE COVERS 1907 - 12 Aug 2004 VOL 141 ISS 7

FILE LAST UPDATED: 11 Aug 2004 (20040811/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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L49 ANSWER 1 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN  
AN 2003:302095 HCAPLUS  
DN 139:159280  
ED Entered STN: 20 Apr 2003  
TI Development of small molecule **Hsp90** inhibitors: Utilizing both forward and reverse chemical genomics for drug identification  
AU **Neckers, Len**  
CS Cell and Cancer Biology Branch, National Cancer Institute, NIH, Rockville, MD, 20850, USA  
SO Current Medicinal Chemistry (2003), 10(9), 733-739  
CODEN: CMCHE7; ISSN: 0929-8673  
PB Bentham Science Publishers Ltd.  
DT Journal; General Review  
LA English  
CC 1-0 (Pharmacology)  
AB A review. **Heat shock protein 90** (**Hsp90**) is a mol. **chaperone** whose association is required for stability and function of multiple mutated, chimeric, and over-expressed signaling **proteins** that promote cancer cell growth and/or survival. **Hsp90** client **proteins** include mutated p53, Bcr-Abl, Raf-1, Akt, HER2/Neu (ErbB2), and HIF-1 $\alpha$ . **Hsp90** inhibitors, by interacting specifically with a single mol. target, cause the destabilization and eventual degradation of **Hsp90** client **proteins**, and they have also shown promising antitumor activity in preclin. model systems. One **Hsp90** inhibitor, 17-AAG, is currently in Phase 1 clin. trial. **Hsp90** inhibitors are unique in that, although they are directed towards a specific mol. target, they simultaneously inhibit multiple signaling pathways on which cancer cells depend for growth and survival. Benzoquinone ansamycin binding to **Hsp90** led to the identification of radicicol as an addnl. **Hsp90** inhibitor. Addnl. target-based screening uncovered **novobiocin** as a third structurally distinct small mol. with **Hsp90** inhibitory properties. Use of **novobiocin**, in turn, led to identification of a previously uncharacterized C-terminal ATP binding site in the **chaperone**. Small mol. inhibitors of **Hsp90** have been very useful in understanding **Hsp90** biol. and in validating this **protein** as a mol. target for anti-cancer drug development.  
ST review antitumor **Hsp90** inhibitor design genomics  
IT **Heat-shock proteins**  
RL: BSU (Biological study, unclassified); BIOL (Biological study) (HSP 90; development of **Hsp90** inhibitors)  
IT Antitumor agents  
Drug design  
Neoplasm  
(development of **Hsp90** inhibitors)  
RE.CNT 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD  
RE  
(1) Alique, R; Embo J 1994, V13, P6099 HCAPLUS  
(2) An, W; Cell Growth Differ 2000, V11, P355 HCAPLUS  
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ED Entered STN: 13 Dec 2000

TI The **heat shock protein 90** antagonist **novobiocin** interacts with a previously unrecognized ATP-binding domain in the carboxyl terminus of the **chaperone**

AU **Marcu, Monica G.**; Chadli, Ahmed; Bouhouche, Ilham; Catelli, Maria; **Neckers, Leonard M.**

CS Department of Cell and Cancer Biology, Medicine Branch, NCI, National Institutes of Health, Rockville, MD, 20850, USA

SO Journal of Biological Chemistry (2000), 275(47), 37181-37186  
CODEN: JBCHA3; ISSN: 0021-9258

PB American Society for Biochemistry and Molecular Biology

DT Journal

LA English

CC 6-3 (General Biochemistry)

AB **Heat shock protein 90** (**Hsp90**), one of the most abundant **chaperones** in eukaryotes, participates in folding and stabilization of signal-transducing mol. including steroid hormone receptors and **protein kinases**. The amino terminus of **Hsp90** contains a non-conventional nucleotide-binding site, related to the ATP-binding motif of bacterial DNA gyrase. The anti-tumor agents geldanamycin and radicicol bind specifically at this site and induce destabilization of **Hsp90**-dependent client **proteins**. We recently demonstrated that the gyrase inhibitor **novobiocin** also interacts with **Hsp90**, altering the affinity of the **chaperone** for geldanamycin and radicicol and causing in vitro and in vivo depletion of key regulatory **Hsp90**-dependent kinases including v-Src, Raf-1, and p185ErbB2. In the present study we used deletion/mutation anal. to identify the site of interaction of **novobiocin** with **Hsp90**, and we demonstrate that the **novobiocin**-binding site resides in the carboxyl terminus of the **chaperone**. Surprisingly, this motif also recognizes ATP, and ATP and **novobiocin** efficiently compete with each other for binding to this region of **Hsp90**. **Novobiocin** interferes with association of the co-**chaperones** Hsc70 and p23 with **Hsp90**. These results identify a second site on **Hsp90** where the binding of small mol. inhibitors can significantly impact the function of this **chaperone**, and they support the hypothesis that both amino- and carboxyl-terminal domains of **Hsp90** interact to modulate **chaperone** activity.

ST **heat shock protein Hsp90**

IT **novobiocin ATP binding site chaperone**

IT **Protein motifs**  
(ATP and **novobiocin**-binding site; **heat shock protein 90** antagonist **novobiocin** interacts with a previously unrecognized ATP-binding domain in carboxyl terminus of **chaperone**)

IT **Heat-shock proteins**  
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)  
(**HSP 90**, recombinant, full-length and deletion mutants; **heat shock protein 90** antagonist **novobiocin** interacts with a previously unrecognized ATP-binding domain in carboxyl terminus of **chaperone**)

IT **Molecular association**  
(**heat shock protein 90** antagonist **novobiocin** interacts with a previously unrecognized ATP-binding domain in carboxyl terminus of **chaperone**)

IT **Phosphoproteins**  
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(hsc 70 (**heat-shock** cognate, 70,000-mol.-weight);

**novobiocin** interferes with association of the co-chaperones  
Hsc70 and p23 with **Hsp90**)

IT **Proteins**, specific or class

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(p23; **novobiocin** interferes with association of the co-chaperones Hsc70 and p23 with **Hsp90**)

IT **303-81-1, Novobiocin**

RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)

(**heat shock protein 90**

antagonist **novobiocin** interacts with a previously unrecognized ATP-binding domain in carboxyl terminus of **chaperone**)

IT 56-65-5, ATP, biological studies

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(**heat shock protein 90-ATP** interaction)

RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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IT **303-81-1, Novobiocin**

RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)

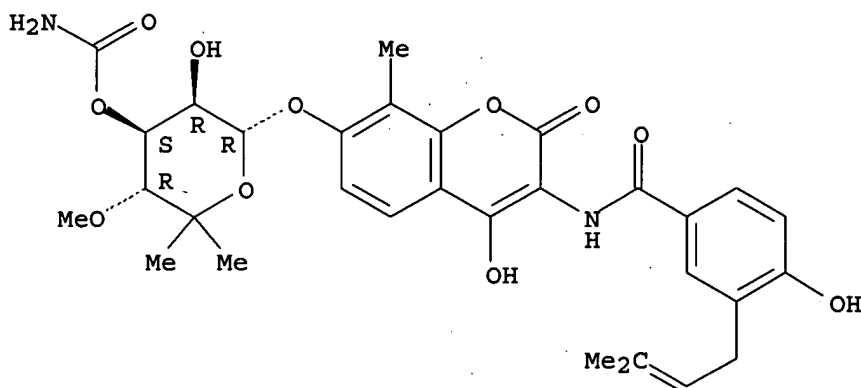
(**heat shock protein 90**

antagonist **novobiocin** interacts with a previously unrecognized ATP-binding domain in carboxyl terminus of **chaperone**)

RN 303-81-1 HCAPLUS

CN Benzamide, N-[7-[[3-O-(aminocarbonyl)-6-deoxy-5-C-methyl-4-O-methyl- $\alpha$ -L-lyxo-hexopyranosyl]oxy]-4-hydroxy-8-methyl-2-oxo-2H-1-benzopyran-3-yl]-4-hydroxy-3-(3-methyl-2-butenyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L49 ANSWER 3 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2000:645839 HCAPLUS

DN 133:203025

ED Entered STN: 15 Sep 2000

TI Method using **coumarin** or a **coumarin** derivative for inhibiting a **chaperone** protein binding to a client protein

IN Marcu, Monica G.; Neckers, Leonard M.; Schulte, Theodor W.

PA United States Dept. of Health and Human Services, USA

SO PCT Int. Appl., 20 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K031-00

CC 1-12 (Pharmacology)

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000053169	A2	20000914	WO 2000-US6482	20000310 <--
	WO 2000053169	C1	20010111		
	W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
EP	1161231	A2	20011212	EP 2000-916277	20000310 <--
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO			
JP	2003523313	T2	20030805	JP 2000-603658	20000310 <--
PRAI	US 1999-124135P	P	19990312	<--	
	WO 2000-US6482	W	20000310		

## CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2000053169	ICM	A61K031-00
AB	A method is provided for inhibiting binding of a <b>chaperone protein</b> with its client <b>protein</b> or client polypeptide. The method comprises contacting <b>coumarin</b> or a <b>coumarin</b> derivative with a <b>chaperone protein</b> , such that the <b>coumarin</b> or the <b>coumarin</b> derivative binds the <b>chaperone protein</b> , which inhibits the <b>chaperone protein</b> from binding its client <b>protein</b> or client polypeptide.	
ST	<b>chaperone protein</b> binding inhibition <b>coumarin</b> deriv	
IT	<b>Heat-shock proteins</b> RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process) ( <b>HSP 90</b> ; <b>coumarin</b> or <b>coumarin</b> derivative for inhibiting binding of <b>chaperone protein</b> to client <b>protein</b> )	
IT	<b>Proteins</b> , general, biological studies RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process) (client, <b>chaperone protein</b> binding to; <b>coumarin</b> or <b>coumarin</b> derivative for inhibiting binding of <b>chaperone protein</b> to client <b>protein</b> )	
IT	Molecular association Mononuclear cell (leukocyte) <b>Protein</b> degradation ( <b>coumarin</b> or <b>coumarin</b> derivative for inhibiting binding of <b>chaperone protein</b> to client <b>protein</b> )	
IT	<b>Chaperonins</b> RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process) ( <b>coumarin</b> or <b>coumarin</b> derivative for inhibiting binding of <b>chaperone protein</b> to client <b>protein</b> )	
IT	Antibiotics ( <b>coumarin</b> ; <b>coumarin</b> or <b>coumarin</b> derivative for inhibiting binding of <b>chaperone protein</b> to client <b>protein</b> )	
IT	Mutation (mutated <b>p53 protein</b> ; <b>coumarin</b> or <b>coumarin</b> derivative for inhibiting binding of <b>chaperone protein</b> to client <b>protein</b> )	
IT	<b>p53 (protein)</b> RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process) (mutated; <b>coumarin</b> or <b>coumarin</b> derivative for inhibiting binding of <b>chaperone protein</b> to client <b>protein</b> )	
IT	<b>Phospholipoproteins</b> RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process) (pp60v-src; <b>coumarin</b> or <b>coumarin</b> derivative for inhibiting binding of <b>chaperone protein</b> to client <b>protein</b> )	
IT	Spleen (splenocyte; <b>coumarin</b> or <b>coumarin</b> derivative for inhibiting binding of <b>chaperone protein</b> to client <b>protein</b> )	
IT	91-64-5, <b>Coumarin</b> 91-64-5D, <b>Coumarin</b> , derivs. 303-81-1, <b>Novobiocin</b> 4434-05-3, <b>Coumermycin A1</b> 39868-96-7, <b>Chlorobiocin</b>	

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(coumarin or coumarin derivative for inhibiting binding of chaperone protein to client protein)

IT 9026-43-1, Serine/threonine kinase 80449-02-1, Tyrosine kinase

137632-09-8 139691-76-2, RAF-1 serine/threonine kinase

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(coumarin or coumarin derivative for inhibiting binding of chaperone protein to client protein)

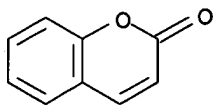
IT 91-64-5, Coumarin 91-64-5D, Coumarin, derivs. 303-81-1, Novobiocin 4434-05-3, Coumermycin A1 39868-96-7, Chlorobiocin

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(coumarin or coumarin derivative for inhibiting binding of chaperone protein to client protein)

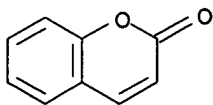
RN 91-64-5 HCAPLUS

CN 2H-1-Benzopyran-2-one (9CI) (CA INDEX NAME)



RN 91-64-5 HCAPLUS

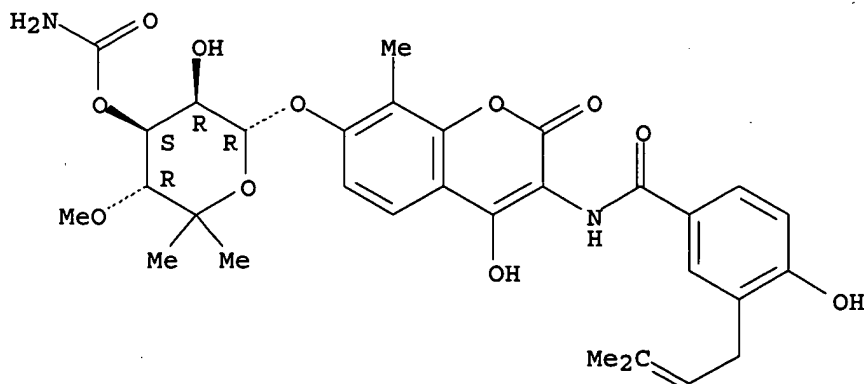
CN 2H-1-Benzopyran-2-one (9CI) (CA INDEX NAME)



RN 303-81-1 HCAPLUS

CN Benzamide, N-[7-[[3-O-(aminocarbonyl)-6-deoxy-5-C-methyl-4-O-methyl- $\alpha$ -L-lyxo-hexopyranosyl]oxy]-4-hydroxy-8-methyl-2-oxo-2H-1-benzopyran-3-yl]-4-hydroxy-3-(3-methyl-2-butenyl) - (9CI) (CA INDEX NAME)

Absolute stereochemistry.

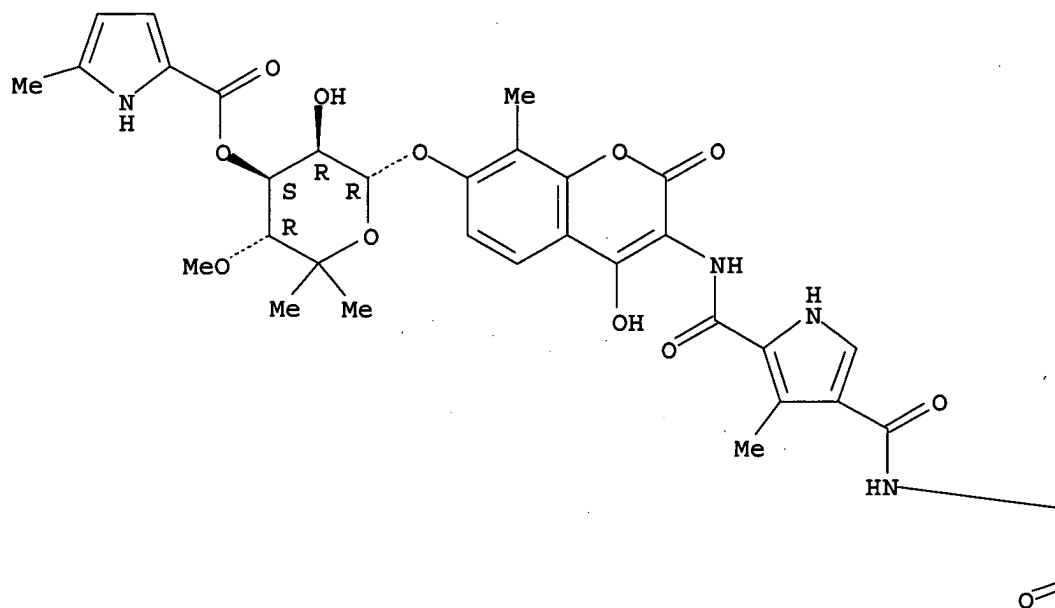


RN 4434-05-3 HCAPLUS

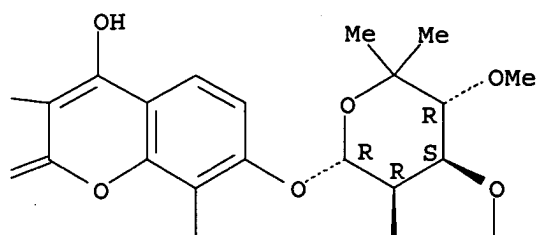
CN 1H-Pyrrole-2,4-dicarboxamide, N,N'-bis[7-[[6-deoxy-5-C-methyl-4-O-methyl-3-O-[(5-methyl-1H-pyrrol-2-yl)carbonyl]- $\alpha$ -L-lyxo-hexopyranosyl]oxy]-4-hydroxy-8-methyl-2-oxo-2H-1-benzopyran-3-yl]-3-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

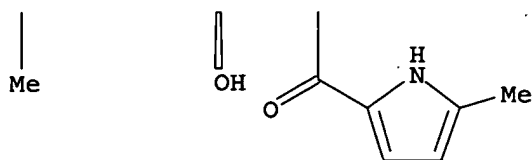
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PAGE 1-B

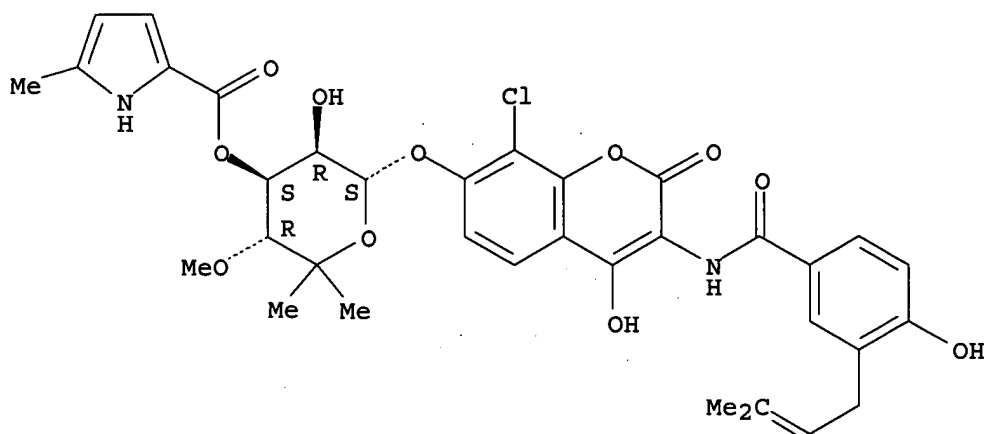


PAGE 2-B



RN 39868-96-7 HCAPLUS  
 CN Benzamide, N-[8-chloro-7-[[6-deoxy-5-C-methyl-4-O-methyl-3-O-[(5-methyl-1H-pyrrol-2-yl)carbonyl]-α-L-lyxo-hexopyranosyl]oxy]-4-hydroxy-2-oxo-2H-1-benzopyran-3-yl]-4-hydroxy-3-(3-methyl-2-butenyl)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



L49 ANSWER 4 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN  
 AN 2000:110237 HCAPLUS  
 DN 133:37820  
 ED Entered STN: 16 Feb 2000  
 TI **Novobiocin and related coumarins and depletion of heat shock protein 90-dependent signaling proteins**  
 AU **Marcu, Monica G.; Schulte, Theodore W.; Neckers, Leonard**  
 CS Department of Cell and Cancer Biology, Medicine Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, 20850, USA  
 SO Journal of the National Cancer Institute (2000), 92(3), 242-248  
 CODEN: JNCIEQ; ISSN: 0027-8874  
 PB Oxford University Press  
 DT Journal  
 LA English  
 CC 1-6 (Pharmacology)  
 AB **Heat shock protein 90 (Hsp90) interacts with and stabilizes several oncogenic protein kinases (e.g., p185erbB2, p60v-src, and Raf-1) and is required for the stability and dominant-neg. function of mutated p53 protein. Two unrelated antibiotics, geldanamycin and radicicol, bind specifically to an atypical nucleotide-binding pocket of Hsp90, a site that shares homol. with the ATP-binding domain of bacterial DNA gyrase B. This interaction leads to destabilization of proteins that interact with Hsp90. Since the nucleotide-binding site of gyrase B is targeted by coumarin**

antibiotics (e.g., **novobiocin**), we investigated whether these drugs can also interact with **Hsp90** and affect its activity. We used immobilized **novobiocin**, geldanamycin, or radicicol to, isolate either endogenous **Hsp90** from cell lysates or **Hsp90** deletion fragments translated in vitro. Effects of the **coumarin** antibiotics **novobiocin**, **chlorobiocin**, and **coumermycin A1** on several **proteins** interacting with **Hsp90** were assessed in vitro and in vivo. **Hsp90** binding to immobilized **novobiocin** was competed by soluble **coumarins** and ATP but not by geldanamycin or radicicol. A carboxy-terminal **Hsp90** fragment bound immobilized **novobiocin** but not immobilized geldanamycin, while a geldanamycin-binding amino-terminal fragment did not bind **novobiocin**. All three **coumarins** markedly reduced cellular levels of p185erbB2, p60v-src, Raf-1, and mutated p53. Furthermore, **novobiocin** reduced Raf-1 levels in the spleens of mice treated with the drug. These **coumarin** antibiotics, particularly **novobiocin**, represent a first-generation alternative to other **Hsp90**-targeting drugs that are not as well tolerated. **Novobiocin's** unique interaction with **Hsp90** identifies an addnl. site on this **protein** amenable to pharmacol. interference with small mols.

- ST **novobiocin coumarin antibiotic Hsp90**  
signaling **protein** antitumor
- IT **Heat-shock proteins**  
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(**HSP 90; novobiocin** and related **coumarins** and depletion of **Hsp90**-dependent signaling **proteins**)
- IT Drug targeting  
(**Hsp90; novobiocin** and related **coumarins** and depletion of **Hsp90**-dependent signaling **proteins**)
- IT Antibiotics  
(**coumarin; novobiocin** and related **coumarins** and depletion of **Hsp90**-dependent signaling **proteins**)
- IT Antitumor agents  
Spleen  
(**novobiocin** and related **coumarins** and depletion of **Hsp90**-dependent signaling **proteins**)
- IT neu (receptor)  
p53 (**protein**)  
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(**novobiocin** and related **coumarins** and depletion of **Hsp90**-dependent signaling **proteins**)
- IT **Phospholipoproteins**  
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(pp60v-src; **novobiocin** and related **coumarins** and depletion of **Hsp90**-dependent signaling **proteins**)
- IT **Proteins, specific or class**  
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(signaling; **novobiocin** and related **coumarins** and depletion of **Hsp90**-dependent signaling **proteins**)
- IT 142805-56-9, Topoisomerase II  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(inhibitors; **novobiocin** and related **coumarins** and depletion of **Hsp90**-dependent signaling **proteins**)
- IT 12772-57-5, Radicicol 30562-34-6, Geldanamycin



RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(novobiocin and related coumarins and depletion of Hsp90-dependent signaling proteins)

IT 303-81-1, Novobiocin 4434-05-3,  
Coumermycin A1 23214-92-8, Doxorubicin 33419-42-0, Etoposide 39868-96-7, Chlorobiocin

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(novobiocin and related coumarins and depletion of Hsp90-dependent signaling proteins)

IT 139691-76-2

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(novobiocin and related coumarins and depletion of Hsp90-dependent signaling proteins)

RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD  
RE

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IT 303-81-1, Novobiocin 4434-05-3,  
Coumermycin A1 39868-96-7, Chlorobiocin

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

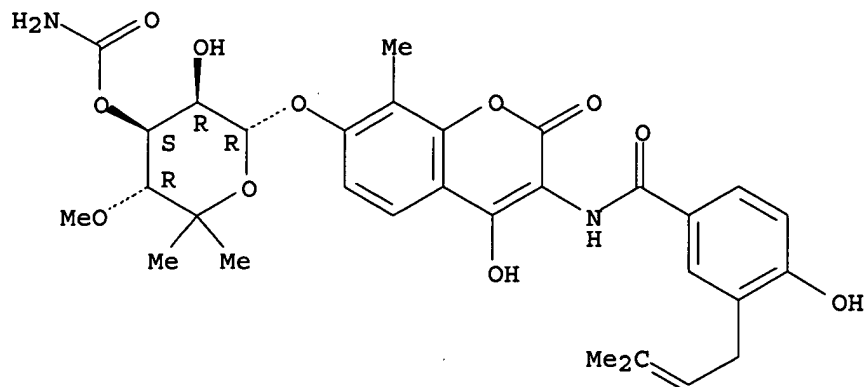
(novobiocin and related coumarins and depletion of Hsp90-dependent signaling proteins)

RN 303-81-1 HCAPLUS

CN Benzamide, N-[7-[[3-O-(aminocarbonyl)-6-deoxy-5-C-methyl-4-O-methyl-

$\alpha$ -L-lyxo-hexopyranosyl]oxy]-4-hydroxy-8-methyl-2-oxo-2H-1-benzopyran-3-yl]-4-hydroxy-3-(3-methyl-2-butenyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

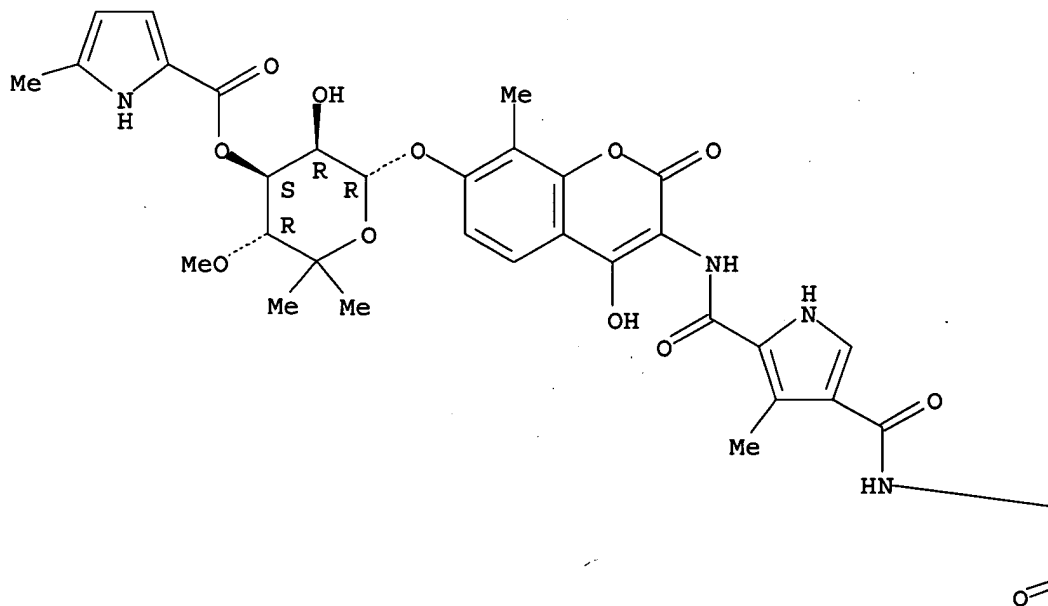


RN 4434-05-3 HCAPLUS

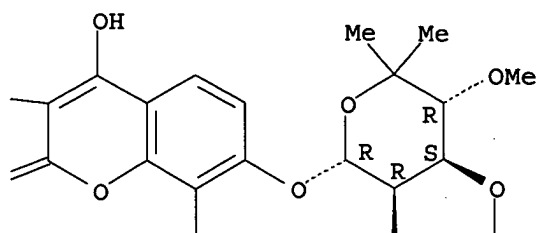
CN 1H-Pyrrole-2,4-dicarboxamide, N,N'-bis[7-[[6-deoxy-5-C-methyl-4-O-methyl-3-O-[(5-methyl-1H-pyrrol-2-yl)carbonyl]- $\alpha$ -L-lyxo-hexopyranosyl]oxy]-4-hydroxy-8-methyl-2-oxo-2H-1-benzopyran-3-yl]-3-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

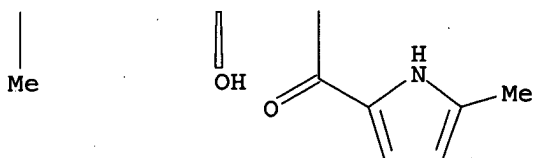
PAGE 1-A



PAGE 1-B

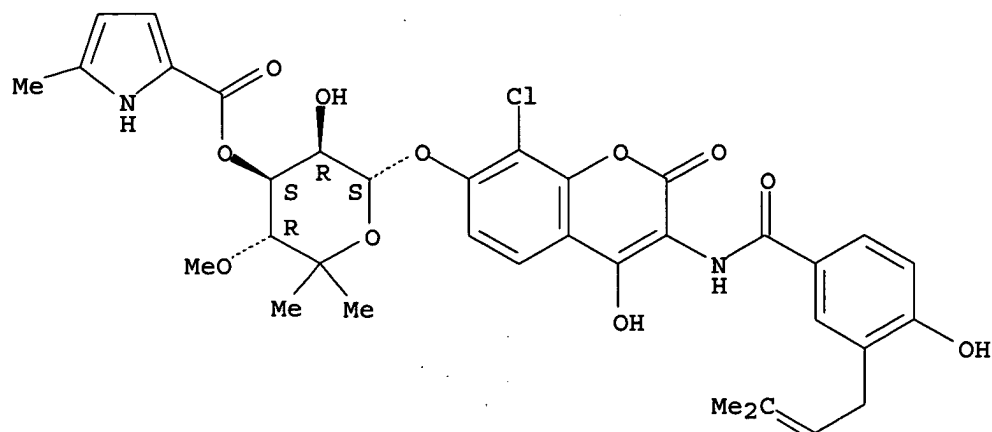


PAGE 2-B



RN 39868-96-7 HCAPLUS  
 CN Benzamide, N-[8-chloro-7-[[6-deoxy-5-C-methyl-4-O-methyl-3-O-[(5-methyl-1H-pyrrol-2-yl)carbonyl]-α-L-lyxo-hexopyranosyl]oxy]-4-hydroxy-2-oxo-2H-1-benzopyran-3-yl]-4-hydroxy-3-(3-methyl-2-butenyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L49 ANSWER 5 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 1999:48608 HCAPLUS

DN 130:119583

ED Entered STN: 25 Jan 1999

TI Inhibitors of the NF- $\kappa$ B factor as activators of HSF and inducers of heat shock proteins for antiproliferative and antiviral therapy

IN Santoro, Maria Gabriella; Rossi, Antonio; Elia, Giuliano

PA Consiglio Nazionale Delle Ricerche, Italy

SO PCT Int. Appl., 16 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM A61K031-00

CC 1-5 (Pharmacology)

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9901117	A2	19990114	WO 1998-EP4066	19980701 <--
WO 9901117	A3	19990401		
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG			
AU 9888545	A1	19990125	AU 1998-88545	19980701 <--
EP 1003492	A2	20000531	EP 1998-940106	19980701 <--
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI			
JP 2002507981	T2	20020312	JP 1999-506339	19980701 <--
PRAI IT 1997-RM392	A	19970701	<--	
WO 1998-EP4066	W	19980701	<--	

#### CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 9901117	ICM	A61K031-00

AB Inhibitors of the NF- $\kappa$ B factor and corresponding pharmaceutically acceptable derivative compds. to be used as activators of the HSF factor for the transcription and translation of heat shock genes, with production of hsp70, particularly with anti-inflammatory,

- anti-proliferative, immuno-suppressive, cytoprotective and antiviral activity. An example of such an inhibitor is 3,4-dichloroisocoumarin.
- ST NFKappaB inhibitor **heat shock** factor activator  
antiproliferative virucide
- IT Transcription factors  
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(HSF (**heat-shock** factor); inhibitors of the NF- $\kappa$ B factor as activators of HSF and inducers of **heat shock proteins** for antiproliferative and antiviral therapy)
- IT **Heat-shock proteins**  
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)  
(HSP 70; inhibitors of the NF- $\kappa$ B factor as activators of HSF and inducers of **heat shock proteins** for antiproliferative and antiviral therapy)
- IT Gene, animal  
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
(HSP70; inhibitors of the NF- $\kappa$ B factor as activators of HSF and inducers of **heat shock proteins** for antiproliferative and antiviral therapy)
- IT Transcription factors  
RL: BSU (Biological study, unclassified); BIOL (Biological study)  
(NF- $\kappa$ B (nuclear factor  $\kappa$ B), inhibitors; inhibitors of the NF- $\kappa$ B factor as activators of HSF and inducers of **heat shock proteins** for antiproliferative and antiviral therapy)
- IT Anti-inflammatory agents  
Antiviral agents  
Cytoprotective agents  
Cytotoxic agents  
DNA viruses  
Human immunodeficiency virus 1  
Immunosuppressants  
Vesicular stomatitis virus  
(inhibitors of the NF- $\kappa$ B factor as activators of HSF and inducers of **heat shock proteins** for antiproliferative and antiviral therapy)
- IT Translation, genetic  
(of **heat-shock** factors; inhibitors of the NF- $\kappa$ B factor as activators of HSF and inducers of **heat shock proteins** for antiproliferative and antiviral therapy)
- IT Transcription, genetic  
(of **heat-shock** genes; inhibitors of the NF- $\kappa$ B factor as activators of HSF and inducers of **heat shock proteins** for antiproliferative and antiviral therapy)
- IT Proliferation inhibition  
(proliferation inhibitors; inhibitors of the NF- $\kappa$ B factor as activators of HSF and inducers of **heat shock proteins** for antiproliferative and antiviral therapy)
- IT RNA viruses  
(single-stranded neg.-polarized; inhibitors of the NF- $\kappa$ B factor as activators of HSF and inducers of **heat shock proteins** for antiproliferative and antiviral therapy)
- IT 402-71-1 2364-87-6 20874-31-1 51050-59-0, 3,4-Dichloroisocoumarin 219787-74-3  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES

## (Uses)

(inhibitors of the NF- $\kappa$ B factor as activators of HSF and inducers of **heat shock proteins** for antiproliferative and antiviral therapy)

IT 37259-58-8, Serine **proteinase**

RL: BSU (Biological study, unclassified); BIOL (Biological study) (inhibitors; inhibitors of the NF- $\kappa$ B factor as activators of HSF and inducers of **heat shock proteins** for antiproliferative and antiviral therapy)

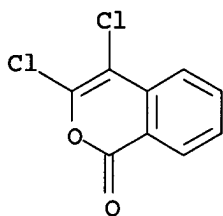
IT 51050-59-0, 3,4-Dichloroisocoumarin

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(inhibitors of the NF- $\kappa$ B factor as activators of HSF and inducers of **heat shock proteins** for antiproliferative and antiviral therapy)

RN 51050-59-0 HCAPLUS

CN 1H-2-Benzopyran-1-one, 3,4-dichloro- (9CI) (CA INDEX NAME)



L49 ANSWER 6 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 1998:508719 HCAPLUS

DN 129:227391

ED Entered STN: 17 Aug 1998

TI Protection from oxidative inactivation of the 20 S proteasome by **heat-shock protein 90**

AU Conconi, Mariangela; Petropoulos, Isabelle; Emod, Istvan; Turlin, Evelyne; Biville, Francis; Friguet, Bertrand

CS Unite de Biochimie Cellulaire, Institut Pasteur, Paris, 75724, Fr.

SO Biochemical Journal (1998), 333(2), 407-415

CODEN: BIJOAK; ISSN: 0264-6021

PB Portland Press Ltd.

DT Journal

LA English

CC 7-3 (Enzymes)

AB **Heat-shock protein 90 (Hsp**

**90)** has been implicated in both protection against oxidative inactivation and inhibition of the multicatalytic **proteinase** (MCP, also known as 20 S proteasome). We report here that the protective and inhibitory effects of **Hsp 90** depend on the activation state of the proteasome. **Hsp 90** (and also  $\alpha$ -crystallin) inhibits the N-Cbz-Leu-Leu-Leu-MCA-hydrolyzing activity (Cbz = benzyloxycarbonyl; MCA = 7-amido-4-methylcoumarin) when the rat liver MCP is in its latent form, but no inhibitory effects are observed when the MCP is in its active form. Metal-catalyzed oxidation of the active MCP inactivates the Ala-Ala-Phe-MCA-hydrolyzing (chymotrypsin-like), N-Boc-Leu-Ser-Thr-Arg-MCA-hydrolyzing (trypsin-like; Boc = t-butyloxycarbonyl), N-Cbz-Leu-Leu-Glu- $\beta$ -naphthylamine-hydrolyzing (peptidylglutamyl-peptide hydrolase) and N-Cbz-Leu-Leu-Leu-MCA-hydrolyzing activities, whereas these activities are actually increased when the MCP is in its latent form. **Hsp 90** protects against oxidative inactivation of the trypsin-like and

N-Cbz-Leu-Leu-Leu-MCA-hydrolyzing activities of the MCP active form, and  $\alpha$ -crystallin protects the trypsin-like activity. The specificity of the Hsp 90-mediated protection was assessed by a quant. anal. of the two-dimensional electrophoretic pattern of MCP subunits before and after oxidation of the MCP, in the presence or absence of Hsp 90. Treatment of the FAO hepatoma cell line with iron and ascorbate was found to inactivate the MCP. Hsp 90 overexpression obtained by challenging the cells with iron was associated with a decreased susceptibility to oxidative inactivation of the MCP trypsin-like activity. Depletion of Hsp 90 by using antisense oligonucleotides resulted in an increased susceptibility to oxidative inactivation of the MCP trypsin-like activity, providing evidence for the physiol. relevance of Hsp 90-mediated protection of the MCP.

ST multicatalytic **proteinase** oxidative inactivation **HSP90**  
; proteasome alpha crystallin metal catalyzed oxidn

IT **Heat-shock proteins**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

(HSP 90; protection from oxidative inactivation of  
20 S proteasome by **heat-shock protein**  
90)

IT Crystallins

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

( $\alpha$ -; protection from oxidative inactivation of 20 S proteasome by  
**heat-shock protein 90**)

IT 140879-24-9, Multicatalytic **proteinase**

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)

(20 S proteasome; protection from oxidative inactivation of 20 S  
proteasome by **heat-shock protein**  
90)

RE.CNT 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD  
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L49 ANSWER 7 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 1996:363736 HCAPLUS

DN 125:52508

ED Entered STN: 22 Jun 1996

TI Are stress **proteins** induced during PUVA therapy?

AU Al-Masaud, A. S.; Cunliffe, W. J.; Holland, D. B.

CS Skin Research Centre, University Leeds, Leeds, LS2 9JT, UK

SO British Journal of Dermatology (1996), 134(5), 892-899

CODEN: BJDEAZ; ISSN: 0007-0963

PB Blackwell

DT Journal

LA English

CC 8-9 (Radiation Biochemistry)

AB **Heat shock** or stress **proteins** are produced

in practically all cell types when they are exposed to temps. a few degrees above normal. Measurement of the skin temperature of patients undergoing psoralen and UVA (PUVA) cabinet treatment for psoriasis revealed that the outer layers of the skin experience a mean temperature rise

of

5-3°C. However, this did not produce a detectable stress response in epidermal samples taken after PUVA treatment. In vitro exposure of epidermis from biopsies or of cultured keratinocytes to a 5-7°C temperature rise produced a **heat shock** response, as measured by an increase in the production of **proteins** of the **HSP90** and **HSP70** families. These results were confirmed by the use of specific monoclonal antibodies. The corresponding mRNAs were also analyzed using labeled probes. In an in vitro system, following simulated PUVA treatment of cultured keratinocytes, increases in the synthesis of **HSP90** and **HSP70** were detected but these increases did not correlate with changes in mRNA levels.

ST psoralen UV stress **protein** psoriasis

IT Psoriasis

(stress **proteins** induced during PUVA therapy in humans)

IT Ultraviolet radiation

(A, stress **proteins** induced during PUVA therapy in humans)

IT **Proteins**, specific or class

RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)

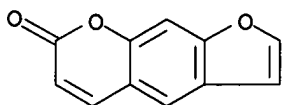


(stress-induced, stress proteins induced during PUVA therapy in humans)

IT 66-97-7, Psoralen  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (stress proteins induced during PUVA therapy in humans)

IT 66-97-7, Psoralen  
 RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (stress proteins induced during PUVA therapy in humans)

RN 66-97-7 HCAPLUS  
 CN 7H-Furo[3,2-g][1]benzopyran-7-one (8CI, 9CI) (CA INDEX NAME)



L49 ANSWER 8 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN  
 AN 1994:100699 HCAPLUS  
 DN 120:100699  
 ED Entered STN: 05 Mar 1994  
 TI 8-Methoxypsoralen plus UVA induces the 72 kDa heat shock protein in organ-cultured normal human skin  
 AU Muramatsu, T.; Yamashina, Y.; Tada, H.; Kobayashi, N.; Yamaji, M.; Ohno, H.; Shirai, T.; Takahashi, A.; Ohinishi, T.  
 CS Dep. Dermatol., Nara Med. Univ., Kashihara, 634, Japan  
 SO Photochemistry and Photobiology (1993), 58(6), 809-12  
 CODEN: PHCBAP; ISSN: 0031-8655  
 DT Journal  
 LA English  
 CC 8-7 (Radiation Biochemistry)  
 AB The proteins induced by heat and other stressors, called heat shock proteins (HSP) or stress proteins, are considered to play a general role in protection from cellular injury. Exposure to UVA (320-400 nm) following application of 8-methoxypsoralen (8-MOP), termed PUVA is commonly used in the field of dermatol. To understand the induction of HSP in PUVA-treated human skin, indirect immunofluorescence using a monoclonal antibody specific for the 72 kDa HSP (HSP 72) was carried out in organ-cultured normal human skin that was treated with PUVA. When the organ-cultured skin was treated at 37° for 1 h with 8-MOP at a final concentration of 10 or 100 µg/mL and exposed to UVA (51.3 kJ/m2), nuclear immunofluorescence of HSP 72 was detected in the epidermal cells 12 h after UVA irradiation. In contrast, the induction of HSP 72 was not detected either by UVA irradiation or 8-MOP treatment. These results suggest that PUVA treatment is one of the stressors for human skin, and DNA damage caused by PUVA induces HSP 72.

ST UVA methoxypsoralen HSP 72 protein skin  
 IT Skin, metabolism  
 (HSP 72 protein expression in human, methoxypsoralen and UVA radiation induction of)

IT Photosensitizers  
 (methoxypsoralen, of HSP 72 protein expression in human skin to UVA radiation)

IT Photodynamic action  
 (of methoxypsoralen, on HSP 72 protein expression in human skin with UVA radiation)

IT Ultraviolet radiation  
(A, **HSP 72 protein** induction by methoxypsoralen and, in human skin)

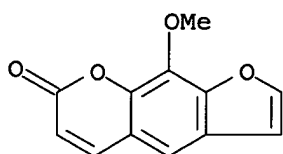
IT **Proteins, specific or class**  
RL: BIOL (Biological study)  
(**HSP 72**, expression of, in human skin, methoxypsoralen and UVA radiation induction of)

IT **298-81-7, 8-MOP**  
RL: BIOL (Biological study)  
(**HSP 72 protein** induction by UVA radiation and, in human skin)

IT **298-81-7, 8-MOP**  
RL: BIOL (Biological study)  
(**HSP 72 protein** induction by UVA radiation and, in human skin)

RN 298-81-7 HCAPLUS

CN 7H-Furo[3,2-g][1]benzopyran-7-one, 9-methoxy- (8CI, 9CI) (CA INDEX NAME)



L49 ANSWER 9 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 1994:95702 HCAPLUS

DN 120:95702

ED Entered STN: 05 Mar 1994

TI **Heat shock** protection against induction of chromatid aberrations by triethylenemelamine in cultured human lymphocytes as affected by caffeine and **novobiocin**

AU Nicolova, Teodora; Petkova, Svetla

CS Inst. Ecol., Sofia, 1113, Bulg.

SO Biologisches Zentralblatt (1993), 112(4), 373-8  
CODEN: BIZNAT; ISSN: 0006-3304

DT Journal

LA English

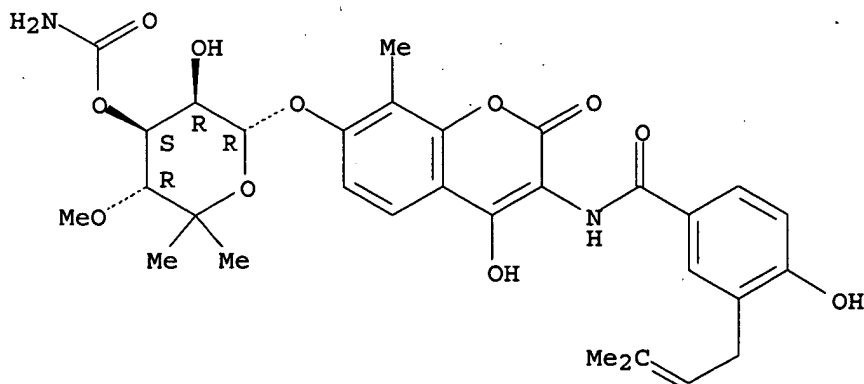
CC 1-12 (Pharmacology)

AB **Novobiocin** and caffeine modulation of protective effects triggered by **heat shock** (hs) against the clastogenic activity of the alkylating agent triethylenemelamine (TEM) in cultured human lymphocytes has been studied. **Heat shock** (hs; 15 min., 41°) prior to challenge treatment with TEM significantly reduced the frequency of metaphases with chromatid aberrations induced by TEM; **novobiocin** treatment before hs slightly reduced hs protection against the clastogen, while **novobiocin** application during the time span between hs and challenge treatment prevented hs-triggered protective effects. The application of caffeine after hs conditioning and before challenge treatment with TEM did not significantly affect hs protection, while caffeine posttreatment in G1 and G2 after hs and TEM-challenging dramatically increased the yield of TEM-induced chromatid aberrations, i.e., prevented any hs protection. Some considerations with respect to the time-limited nature of hs protection and the involvement of hs **proteins** and chromatin conformation in the hs response are discussed.

ST triethylenemelamine chromatid aberration lymphocyte **heat shock**; caffeine triethylenemelamine chromatid lymphocyte **heat shock**; **novobiocin** triethylenemelamine chromatid lymphocyte **heat shock**

- IT Chromatid  
(aberrations, by triethylenemelamine in cultured human lymphocytes, **heat shock** protection against, caffeine and **novobiocin** modulation of)
- IT Lymphocyte  
(chromatid aberrations by triethylenemelamine in cultured human, **heat shock** protection against induction of, caffeine and **novobiocin** modulation of)
- IT Shock  
(heat, protection against induction of chromatid aberrations by triethylenemelamine in cultured human lymphocytes by, caffeine and **novobiocin** modulation of)
- IT Drug interactions  
(of caffeine and **novobiocin**, with **heat shock** protective effects against induction of chromatid aberrations by triethylenemelamine in cultured human lymphocytes)
- IT Temperature effects, biological  
(**heat, shock** from, protection against induction of chromatid aberrations by triethylenemelamine in cultured human lymphocytes by, caffeine and **novobiocin** modulation of)
- IT 51-18-3, Triethylenemelamine  
RL: BIOL (Biological study)  
(chromatid aberrations by, in cultured human lymphocytes, **heat shock** protection against, caffeine and **novobiocin** modulation of)
- IT 58-08-2, Caffeine, biological studies 303-81-1, **Novobiocin**  
RL: BIOL (Biological study)  
(**heat shock** protection against induction of chromatid aberrations by triethylenemelamine in cultured human lymphocytes modulation by)
- IT 303-81-1, **Novobiocin**  
RL: BIOL (Biological study)  
(**heat shock** protection against induction of chromatid aberrations by triethylenemelamine in cultured human lymphocytes modulation by)
- RN 303-81-1 HCAPLUS
- CN Benzamide, N-[7-[[3-O-(aminocarbonyl)-6-deoxy-5-C-methyl-4-O-methyl- $\alpha$ -L-lyxo-hexopyranosyl]oxy]-4-hydroxy-8-methyl-2-oxo-2H-1-benzopyran-3-yl]-4-hydroxy-3-(3-methyl-2-butenyl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



ED Entered STN: 04 Oct 1992

TI Natural inhibitors of germination and growth. VI. Detection of a carboxy-terminal fragment of the **heat shock protein HSP 70** after **coumarin** treatment

AU Oster, U.; Kardinal, C.; Burghardt, H.; Werner, B.; Lottspeich, F.; Ruediger, W.

CS Bot. Inst., Univ. Muenchen, Munich, D-8000/19, Germany

SO Journal of Plant Physiology (1992), 140(1), 110-15  
CODEN: JPPHEY; ISSN: 0176-1617

DT Journal

LA English

CC 11-3 (Plant Biochemistry)

AB To elucidate the mechanism of germination inhibition by **coumarin**, **protein** patterns of dry seeds, seedlings germinated for 48 h, and **coumarin**-treated seeds from cress (*Lepidium sativum*) were investigated. The **coumarin**-treated seeds failed to germinate and showed a strong 32 kDa **protein** band that was not observed in germinated seedlings but was found in dry seeds. This **protein** was isolated, and the first 16 amino acids of the N-terminus were sequenced. The sequence showed a 100% identity with the amino acids 396-421 of the **heat-shock protein HSP 70**. Apparently, inhibition of **HSP 70** proteolysis is involved in the inhibition of germination by **coumarin**.

ST **heat shock protein** cress germination;  
**coumarin** proteolysis germination inhibition

IT Germination  
(**coumarin** inhibition of, **heat-shock protein HSP 70** proteolysis in cress seeds in)

IT Seed  
(**heat-shock protein** fragment of **coumarin**-treated, of cress)

IT *Lepidium sativum*  
(**heat-shock protein** fragment of germination inhibitor-treated seeds of)

IT **Protein** sequences  
(of **HSP 70** fragment from **coumarin**-treated cress seed, N-terminus)

IT **Proteins, specific or class**  
RL: BIOL (Biological study)  
(**HSP 70**, proteolysis of, in cress seeds treated with germination inhibitor)

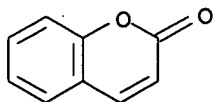
IT 91-64-5, 2H-1-Benzopyran-2-one  
RL: BIOL (Biological study)  
(germination inhibition by, **heat-shock HSP 70 protein** proteolysis in)

IT 143222-50-8P  
RL: SPN (Synthetic preparation); PREP (Preparation)  
(preparation of)

IT 91-64-5, 2H-1-Benzopyran-2-one  
RL: BIOL (Biological study)  
(germination inhibition by, **heat-shock HSP 70 protein** proteolysis in)

RN 91-64-5 HCAPLUS

CN 2H-1-Benzopyran-2-one (9CI) (CA INDEX NAME)



L49 ANSWER 11 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN  
AN 1988:626487 HCAPLUS  
DN 109:226487  
ED Entered STN: 24 Dec 1988  
TI **Heat-shock** response in *Legionella pneumophila*  
AU Lema, Michael W.; Brown, Arnold; Butler, Charles A.; Hoffman, Paul S.  
CS Res. Serv., W. J. B. Dorn Veterans Hosp., Columbia, SC, 29201, USA  
SO Canadian Journal of Microbiology (1988), 34(10), 1148-53  
CODEN: CJMIAZ; ISSN: 0008-4166  
DT Journal  
LA English  
CC 10-2 (Microbial Biochemistry)  
AB The **heat-shock** response of *L. pneumophila* was examined by radiolabeling bacterial cell **proteins** with [35S]methionine following a temperature shift from 30 to 42°. Five **heat-shock proteins** were identified as having mol. masses of 17, 60, 70, 78, and 85 kilodaltons (kDa). The 85- and 60-kDa **proteins** were equally distributed between supernatant and pellet fractions following ultracentrifugation at 100,000 + g, the 70- and 78-kDa **proteins** were found primarily in the supernatant, and the 17-kDa **protein** was found primarily in the pellet. Synthesis of subsets of the **heat-shock proteins** could be stimulated by novobiocin, patulin, or puromycin. EtOH, an effector of the **heat-shock** response in other microorganisms, had little effect on *L. pneumophila*, even at the highest concentration tolerated by the bacterial cells (1.9%). Finally, the 60-kDa **heat-shock protein** of *L. pneumophila* was immunol. cross-reactive with a polyclonal antibody prepared to the *Escherichia coli* groEL **protein**. However, a mouse monoclonal antibody reactive with the 60-kDa **protein** of all legionellae tested did not cross-react with the *E. coli* groEL **protein**, suggesting that the *Legionella* 60-kDa **protein** contains common and unique epitopes.  
ST **heat shock protein** *Legionella*  
IT *Legionella pneumophila*  
(**heat-shock** response in)  
IT **Proteins, specific or class**  
RL: FORM (Formation, nonpreparative)  
(**heat-shock**, formation of, by *Legionella pneumophila*)

L49 ANSWER 12 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN  
AN 1988:567088 HCAPLUS  
DN 109:167088  
ED Entered STN: 12 Nov 1988  
TI The role of **heat shock proteins** in differentiation of *Trypanosoma brucei*  
AU Davis, Charles E.; Guiney, D. G.; Colmerauer, M. E. M.  
CS Sch. Med., UCSD, San Diego, CA, 92103, USA  
SO UCLA Symposium on Molecular and Cellular Biology, New Series (1987), 42(Mol. Strategies Parasit. Invasion), 169-79  
CODEN: USMBD6; ISSN: 0735-9543  
DT Journal  
LA English  
CC 10-3 (Microbial Biochemistry)  
AB Near peak parasitemia, *T. brucei* differentiates from rapidly-replicating long-slender forms to short-stumpies that do not replicate in the mammal but are necessary to infect the tsetse. Indomethacin accelerates differentiation, whereas theophylline blocks the process, in association with changes in intratrypanosomal cAMP. In an attempt to find natural regulators and markers of differentiation, lysates of long-slenders,

short-stumpies and procyclics (insect mid-gut form) were probed for **heat-shock proteins (hsp)**, because trypanosomes experience several temperature changes during their life cycle. Anti-chicken **hsp-70** detected prominent 70 K dalton bands in immunoblots of each morphol. form. Furthermore, **novobiocin**, which blocks the **heat-shock** response of *Drosophila*, also blocks differentiation of *T. brucei* in mice. In 3 expts., *T. brucei* populations in treated mice never completely differentiated and mean parasitemia never remitted, whereas control mice experienced 2 cycles of parasitemia. Thus, differentiation of *T. brucei*, which moderates parasitemia and is essential to the life cycle, may be triggered by **hsp** induced by mammalian fever.

ST Trypanosoma differentiation **heat shock protein**  
 IT Trypanosoma brucei  
     (differentiation of, **heat-shock protein hsp70** in)  
 IT Microorganism development  
     (of Trypanosoma brucei, **heat shock protein hsp70** in relation to)  
 IT **Proteins, specific or class**  
 RL: BIOL (Biological study)  
     (**hsp 70**, in differentiation of Trypanosoma brucei)

L49 ANSWER 13 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 1984:504070 HCAPLUS

DN 101:104070

ED Entered STN: 29 Sep 1984

TI Teratogens induce a subset of small **heat shock proteins** in *Drosophila* primary embryonic cell cultures

AU Buzin, Carolyn H.; Bournias-Vardiabasis, Nicole

CS Div. Cytogenet. Cytol., City Hope Med. Cent., Duarte, CA, 91010, USA

SO Proceedings of the National Academy of Sciences of the United States of America (1984), 81(13), 4075-9

CODEN: PNASA6; ISSN: 0027-8424

DT Journal

LA English

CC 1-12 (**Pharmacology**)

Section cross-reference(s): 2, 4, 12

AB *Drosophila* Embryonic cells placed into culture just after gastrulation differentiate in vitro over the next 24 h. A number of drugs that are teratogenic in mammalian systems have been found to inhibit muscle or neuron differentiation (or both) in these developing cultures. By two-dimensional gel electrophoresis, the effects of these drugs on **protein** synthesis in embryonic cells were examined. For 9 teratogens tested, cells treated for 20 h with the drug show a dramatic induction of three **proteins** of about 20 kilodaltons, in addition to the normal **proteins** synthesized by untreated cells. Three teratogens as well as all 8 nonteratogens tested did not show this induction. The induced **proteins** appear to be identical to 3 or the **heat-shock proteins (hsp 23, 22a, and 22b)**, as shown by electrophoresis mobilities and peptide mapping by partial proteolysis. A 37° **heat shock** of the embryonic cells produces the full complement of **heat-shock proteins**, whereas drug-treated cells induce only the subset **hsp 23, 22a, and 22b** but not **hsp 26 or 27**.  $\beta$ -Ecdysterone [5289-74-7], the *Drosophila* molting hormone, also inhibits embryonic differentiation and induces **hsp 23, 22a, and 22b**, a partial subset of the **heat shock proteins (hsp 22, 23, 26, and 27)** induced by the hormone in imaginal discs and some *Drosophila* continuous cell lines. Dose-response studies of several drugs show a correlation between the degree of inhibition of differentiation and the level of induction of **hsp 23, 22a, and 22b**. The induction of **heat**

**shock proteins** by drugs may reflect specific types of stress that can also give rise to teratogenesis.

ST teratogen **Drosophila heat shock protein**

IT **Drosophila** (insect)  
(**heat-shock proteins** induction in embryonic cells of, by teratogens)

IT Teratogens  
(**Drosophila embryonic cell heat shock protein** response to)

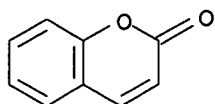
IT 50-02-2 50-49-7 53-06-5 56-53-1 57-41-0 57-83-0, biological studies 58-08-2, biological studies 58-18-4 59-05-2 60-80-0 63-74-1 64-17-5, biological studies 64-77-7 67-68-5, biological studies 76-74-4 81-07-2 **91-64-5** 320-67-2 915-67-3 5289-74-7

RL: BIOL (Biological study)  
(**Drosophila embryonic cell heat shock protein** response to)

IT **91-64-5**  
RL: BIOL (Biological study)  
(**Drosophila embryonic cell heat shock protein** response to)

RN 91-64-5 HCAPLUS

CN 2H-1-Benzopyran-2-one (9CI) (CA INDEX NAME)



L49 ANSWER 14 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 1983:65128 HCAPLUS

DN 98:65128

ED Entered STN: 12 May 1984

TI The induction of a subset of **heat-shock proteins** by drugs that inhibit differentiation in **Drosophila** embryonic cell cultures

AU Buzin, Carolyn H.; Bournias-Vardiabasis, Nicole

CS Div. Cytogenet. Cytol., City of Hope Med. Cent., Duarte, CA, 91010, USA

SO Heat Shock: Bact. Man, [Pap. Meet.] (1982), 387-94. Editor(s): Schlessinger, Milton J.; Ashburner, Michael; Tissières, Alfred. Publisher: Cold Spring Harbor Lab., Cold Spring Harbor, N. Y. CODEN: 49ARAW

DT Conference

LA English

CC 1-4 (Pharmacology)  
Section cross-reference(s): 2

AB In **Drosophila** primary embryonic cells, 8 of 10 drugs tested that inhibit differentiation stimulated formation of 3 **heat-shock proteins** with the same electrophoretic mobilities as **hsp23**, **hsp22a**, and **hsp22b proteins** but did not affect the formation of other **heat-shock proteins**; **heat shock** of the embryonic cells induced the full complement of **heat-shock proteins**. In contrast, 7 drugs that do not inhibit differentiation did not induce the 3 **proteins**. A mild heat treatment (that induces **heat-shock proteins**) partially protects cells from the inhibition of differentiation caused by a subsequent 2-h period of hyperthermia or drug treatment. Since the formation of a subset of **heat-shock proteins** can be separated from that of the entire complement of **heat-**

**shock proteins**, studies on the function and control of **hsp22** and **hsp23** can be carried out in the absence of the other **heat-shock proteins**. The **hsp23**, **hsp22a**, and **hsp22b proteins** may be involved in the protective effect of mild heat pretreatment.

ST drug embryo differentiation **protein** *Drosophila*; **heat shock protein** embryo drug

IT *Drosophila* (insect)  
(embryonic cells of, **heat-shock proteins** induction by drugs and heat in, differentiation inhibition in relation to)

IT Embryo  
(**heat-shock proteins** induction by drugs and heat in, of *Drosophila*, differentiation inhibition in relation to)

IT Heat, biological effects  
(**heat-shock proteins** induction by, in embryonic cells of *Drosophila*, differentiation inhibition in relation to)

IT Pharmacology  
(**heat-shock proteins** of embryonic cells of *Drosophila* response in, differentiation inhibition in relation to)

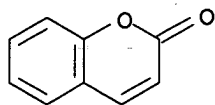
IT **Proteins**  
RL: BIOL (Biological study)  
(**heat-shock**, of embryonic cells of *Drosophila*, drugs and heat induction of, differentiation inhibition in relation to)

IT 50-02-2 53-06-5 56-53-1 57-41-0 57-83-0, biological studies  
58-08-2, biological studies 58-18-4 59-05-2 60-80-0 63-74-1  
64-77-7 67-68-5, biological studies 76-74-4 81-07-2 91-64-5  
915-67-3 5289-74-7  
RL: BIOL (Biological study)  
(**heat-shock proteins** of embryonic cells of *Drosophila* response to, differentiation inhibition in relation to)

IT 91-64-5  
RL: BIOL (Biological study)  
(**heat-shock proteins** of embryonic cells of *Drosophila* response to, differentiation inhibition in relation to)

RN 91-64-5 HCAPLUS

CN 2H-1-Benzopyran-2-one (9CI) (CA INDEX NAME)



L49 ANSWER 15 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 1983:50260 HCAPLUS

DN 98:50260

ED Entered STN: 12 May 1984

TI The **heat-shock** phenomenon in bacteria - a protection against DNA relaxation?

AU Travers, Andrew A.; Mace, Hilary A. F.

CS Lab. Mol. Biol., Med. Res. Counc. Cent., Cambridge, CB2 2QH, UK

SO Heat Shock: Bact. Man, [Pap. Meet.] (1982), 127-30. Editor(s): Schlesinger, Milton J.; Ashburner, Michael; Tissieres, Alfred. Publisher: Cold Spring Harbor Lab., Cold Spring Harbor, N. Y.  
CODEN: 49ARAW

DT Conference

LA English

CC 10-5 (Microbial Biochemistry)

AB In organisms as diverse as *Escherichia coli* and humans, cells respond to



rapid temperature rises of 5-15° by inducing a transient production of **heat-shock proteins**. Also, agents that disrupt chromosomal structure might induce the synthesis of some or all **heat-shock proteins**. **Coumermycin A1**, an inhibitor of the B subunit of DNA topoisomerase II, induces the synthesis of a small set of **proteins** in *E. coli* cells sensitive to the drug. With 1 exception, all coumeromycin-induced **proteins** corresponded to **heat-shock proteins**. In *Drosophila*, gene **hsp70** **heat-shock protein** appears to be associated with the interband regions of polytene chromosomes, suggesting that the **heat-shock protein** may also play a role in stabilizing chromosome structure in eukaryotes.

ST **heat shock protein** bacteria DNA relaxation  
 IT Bacteria  
   *Escherichia coli*  
     (**heat-shock proteins** of, DNA relaxation  
       in relation to)  
 IT Deoxyribonucleic acids  
   RL: PROC (Process)  
     (relaxation of, in bacteria, **heat-shock**  
       **protein** in relation to)  
 IT **Proteins**  
   RL: BIOL (Biological study)  
     (**heat-shock**, in bacteria, DNA relaxation in  
       relation to)

=> => fil biosis

FILE 'BIOSIS' ENTERED AT 09:27:57 ON 12 AUG 2004  
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FILE COVERS 1969 TO DATE.

CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT  
 FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 11 August 2004 (20040811/ED)

FILE RELOADED: 19 October 2003.

=> =>

=> d his l54-

(FILE 'REGISTRY' ENTERED AT 09:24:39 ON 12 AUG 2004)

FILE 'HCAPLUS' ENTERED AT 09:24:50 ON 12 AUG 2004

FILE 'BIOSIS' ENTERED AT 09:25:17 ON 12 AUG 2004

          E MARCU M/AU  
 L54      17 S E3,E9,E10  
           E NECKERS L/AU  
 L55      301 S E3-E11  
           E SCHULTE T/AU  
 L56      69 S E3,E8,E10-E12  
 L57      349 S L54-L56  
 L58      64 S (HSP? OR HEAT SHOCK) AND L57  
 L59      35 S ?CHAPERON? AND L57  
 L60      67 S L58,L59  
 L61      7 S L60 AND L9,L12,L13  
 L62      7 S L60 AND L19  
 L63      0 S L60 AND L20  
 L64      0 S L60 AND L21  
 L65      7 S L61,L62  
 L66      7 S L65 AND ?PROTEIN?

L67 7 S L66 AND 90  
L68 7 S L66-L67

FILE 'BIOSIS' ENTERED AT 09:27:57 ON 12 AUG 2004

L69 7 S L68 AND L54-L68  
E MARCU M/AU  
L70 2 S E3,E4 AND L69  
L71 11 S E3,E4 NOT L70  
L72 7 S L69,L70

=> d all tot

L72 ANSWER 1 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN  
AN 2003:484752 BIOSIS  
DN PREV200300484752  
TI The C-terminal half of **heat shock protein**  
90 represents a second site for pharmacologic intervention in  
**chaperone** function.  
AU **Marcu, Monica G.; Neckers, Leonard M.** [Reprint Author]  
CS Cell and Cancer Biology Branch, Center for Cancer Research, National  
Cancer Institute, 9610 Medical Center Drive, Suite 300, Rockville, MD,  
20850, USA  
len@helix.nih.gov  
SO Current Cancer Drug Targets, (October 2003) Vol. 3, No. 5, pp. 343-347.  
print.  
ISSN: 1568-0096 (ISSN print).  
DT Article  
General Review; (Literature Review)  
LA English  
ED Entered STN: 15 Oct 2003  
Last Updated on STN: 15 Oct 2003  
CC Biochemistry studies - General 10060  
Biochemistry studies - Nucleic acids, purines and pyrimidines 10062  
Enzymes - General and comparative studies: coenzymes 10802  
Pathology - Therapy 12512  
Pharmacology - General 22002  
Neoplasms - Pathology, clinical aspects and systemic effects 24004  
Neoplasms - Therapeutic agents and therapy 24008  
IT Major Concepts  
Enzymology (Biochemistry and Molecular Biophysics); Pharmacology; Tumor  
Biology  
IT Diseases  
cancer: neoplastic disease  
Neoplasms (MeSH)  
IT Chemicals & Biochemicals  
cisplatin: antineoplastic-drug; **heat shock**  
**protein 90**: C-terminal, molecular **chaperone**  
; molybdate; **novobiocin**: enzyme inhibitor-drug; nucleotide;  
**protein kinase** [EC 2.7.1.37]; radicicol: antineoplastic-drug,  
enzyme inhibitor-drug; steroid receptors; transcription factors  
IT Miscellaneous Descriptors  
cell growth; cell survival  
RN 15663-27-1 (cisplatin)  
11116-47-5 (molybdate)  
303-81-1 (**novobiocin**)  
9026-43-1Q (**protein kinase**)  
80449-02-1Q (**protein kinase**)  
134549-83-0Q (**protein kinase**)  
372092-80-3Q (**protein kinase**)  
9026-43-1 (**protein kinase**)  
9026-43-1Q (EC 2.7.1.37)  
80449-02-1Q (EC 2.7.1.37)  
134549-83-0Q (EC 2.7.1.37)

372092-80-3Q (EC 2.7.1.37)  
9026-43-1 (EC 2.7.1.37)  
12772-57-5 (radicicol)

L72 ANSWER 2 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN  
AN 2003:238051 BIOSIS  
DN PREV200300238051  
TI Development of small molecule **Hsp90** inhibitors: Utilizing both  
forward and reverse chemical genomics for drug identification.  
AU **Neckers, Len** [Reprint Author]  
CS Cell and Cancer Biology Branch, National Cancer Institute, NIH, 9610  
Medical Center Drive, Suite 300, Rockville, MD, 20850, USA  
len@helix.nih.gov  
SO Current Pharmaceutical Design, (May 2003) Vol. 10, No. 9, pp. 733-739.  
print.  
ISSN: 1381-6128 (ISSN print).  
DT Article  
General Review; (Literature Review)  
LA English  
ED Entered STN: 14 May 2003  
Last Updated on STN: 14 May 2003  
CC Biochemistry studies - Proteins, peptides and amino acids 10064  
Pathology - Therapy 12512  
Pharmacology - General 22002  
Pharmacology - Clinical pharmacology 22005  
Neoplasms - Pathology, clinical aspects and systemic effects 24004  
Neoplasms - Therapeutic agents and therapy 24008  
IT Major Concepts  
Pharmacology; Tumor Biology  
IT Diseases  
cancer: neoplastic disease  
Neoplasms (MeSH)  
IT Chemicals & Biochemicals  
17-allylaminogeldanamycin [17-AAG]: antineoplastic-drug, phase I  
clinical trial; Akt; Bcr-Abl; HER2/Neu [ErbB2]; HIF-1-alpha; Raf-1;  
benzoquinone ansamycin; **heat shock protein**  
**90 [Hsp90]**: carboxy-terminal ATP binding site,  
molecular **chaperone**; **novobiocin**:  
antineoplastic-drug, enzyme inhibitor-drug; p53; radicicol:  
antineoplastic-drug; small molecule **heat shock**  
**protein 90** inhibitors [small molecule **Hsp90**  
inhibitors]: antineoplastic-drug  
IT Methods & Equipment  
drug identification: laboratory techniques  
IT Miscellaneous Descriptors  
forward chemical genomics; reverse chemical genomics; signaling  
pathways  
RN 75747-14-7 (17-allylaminogeldanamycin)  
75747-14-7 (17-AAG)  
**303-81-1 (novobiocin)**  
12772-57-5 (radicicol)

L72 ANSWER 3 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN  
AN 2002:418975 BIOSIS  
DN PREV200200418975  
TI Curcumin, an antioxidant and anti-inflammatory phytochemical, depletes  
**Hsp90**-dependent signaling **proteins** without direct  
binding to the **chaperone**.  
AU **Marcu, Monica G.** [Reprint author]; **Neckers, Len**  
[Reprint author]  
CS NIH, NCI, Rockville, MD, USA  
SO Proceedings of the American Association for Cancer Research Annual  
Meeting, (March, 2002) Vol. 43, pp. 964. print.

Meeting Info.: 93rd Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA. April 06-10, 2002.  
ISSN: 0197-016X.

DT Conference; (Meeting)  
Conference; Abstract; (Meeting Abstract)  
LA English  
ED Entered STN: 7 Aug 2002  
Last Updated on STN: 7 Aug 2002  
CC General biology - Symposia, transactions and proceedings 00520  
Biochemistry studies - Nucleic acids, purines and pyrimidines 10062  
Biochemistry studies - Proteins, peptides and amino acids 10064  
Pathology - Therapy 12512  
Metabolism - General metabolism and metabolic pathways 13002  
Pharmacology - General 22002  
Pharmacology - Drug metabolism and metabolic stimulators 22003  
Pharmacology - Connective tissue, bone and collagen-acting drugs 22012  
Pharmacology - Immunological processes and allergy 22018  
Chemotherapy - General, methods and metabolism 38502  
IT Major Concepts  
Metabolism; Pharmacology  
IT Chemicals & Biochemicals  
ATP; Akt: **heat shock protein 90**  
-dependent kinase, regulation; ErbB2: **heat shock protein 90**-dependent kinase, regulation; Raf1:  
**heat shock protein 90**-dependent  
kinase, regulation; **chaperone protein**: binding;  
curcumin: antiinflammatory-drug, immunologic-drug, metabolic-drug,  
pharmacodynamics; geldanamycin: antiinfective-drug; **heat shock protein 90 [Hsp90]**;  
novobiocin: antiinfective-drug, enzyme inhibitor-drug; p53:  
mutation, regulation; signaling **protein**: regulation  
IT Miscellaneous Descriptors  
Meeting Abstract  
RN 56-65-5Q (ATP)  
42530-29-0Q (ATP)  
94587-45-8Q (ATP)  
111839-44-2Q (ATP)  
458-37-7 (curcumin)  
30562-34-6 (geldanamycin)  
303-81-1 (novobiocin)  
L72 ANSWER 4 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN  
AN 2001:48490 BIOSIS  
DN PREV200100048490  
TI The **heat shock protein 90**  
antagonist novobiocin interacts with a previously unrecognized  
ATP-binding domain in the carboxyl terminus of the **chaperone**.  
AU Marcu, Monica G.; Chadli, Ahmed; Bouhouche, Ilham; Catelli,  
Maria; Neckers, Leonard M. [Reprint author]  
CS Department of Cell and Cancer Biology, Medicine Branch, NCI, National  
Institutes of Health, Rockville, MD, 20850, USA  
len@helix.nih.gov  
SO Journal of Biological Chemistry, (November 24, 2000) Vol. 275, No. 47, pp.  
37181-37186. print.  
CODEN: JBCHA3. ISSN: 0021-9258.  
DT Article  
LA English  
ED Entered STN: 24 Jan 2001  
Last Updated on STN: 12 Feb 2002  
AB **Heat shock protein 90** (**Hsp90**), one of the most abundant **chaperones** in  
eukaryotes, participates in folding and stabilization of  
signal-transducing molecules including steroid hormone receptors and

**protein kinases.** The amino terminus of **Hsp90** contains a non-conventional nucleotide-binding site, related to the ATP-binding motif of bacterial DNA gyrase. The anti-tumor agents geldanamycin and radicicol bind specifically at this site and induce destabilization of **Hsp90**-dependent client **proteins**. We recently demonstrated that the gyrase inhibitor **novobiocin** also interacts with **Hsp90**, altering the affinity of the **chaperone** for geldanamycin and radicicol and causing in vitro and in vivo depletion of key regulatory **Hsp90**-dependent kinases including v-Src, Raf-1, and p185ErbB2. In the present study we used deletion/mutation analysis to identify the site of interaction of **novobiocin** with **Hsp90**, and we demonstrate that the **novobiocin**-binding site resides in the carboxyl terminus of the **chaperone**. Surprisingly, this motif also recognizes ATP, and ATP and **novobiocin** efficiently compete with each other for binding to this region of **Hsp90**. **Novobiocin** interferes with association of the co-**chaperones** Hsc70 and p23 with **Hsp90**. These results identify a second site on **Hsp90** where the binding of small molecule inhibitors can significantly impact the function of this **chaperone**, and they support the hypothesis that both amino- and carboxyl-terminal domains of **Hsp90** interact to modulate **chaperone** activity.

- CC Biochemistry studies - Nucleic acids, purines and pyrimidines 10062  
 Biochemistry studies - General 10060  
 Enzymes - General and comparative studies: coenzymes 10802  
 Pathology - Therapy 12512  
 Pharmacology - General 22002  
 Neoplasms - Therapeutic agents and therapy 24008
- IT Major Concepts  
 Biochemistry and Molecular Biophysics; Pharmacology
- IT Chemicals & Biochemicals  
 ATP; DNA gyrase; Hsc70; geldanamycin: antineoplastic-drug; **heat shock protein 90**; molecular **chaperone**: ATP-binding domain; **novobiocin**: enzyme inhibitor; p23; radicicol: antineoplastic-drug
- IT Miscellaneous Descriptors  
**protein-drug** interaction; signal transduction
- RN 56-65-5Q (ATP)  
 42530-29-0Q (ATP)  
 94587-45-8Q (ATP)  
 111839-44-2Q (ATP)  
 30562-34-6 (geldanamycin)  
 303-81-1 (**novobiocin**)  
 12772-57-5 (radicicol)
- L72 ANSWER 5 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN  
 AN 2000:252235 BIOSIS  
 DN PREV2000000252235  
 TI **Novobiocin, a heat shock protein 90 (HSP90) inhibitor, interacts with a previously uncharacterized ATP-binding domain in the C-terminus of the chaperone.**
- AU Marcu, M. G. [Reprint author]; Neckers, L. M. [Reprint author]
- CS National Cancer Inst, Rockville, MD, USA  
 SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2000) No. 41, pp. 312. print.  
 Meeting Info.: 91st Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA. April 01-05, 2000.  
 ISSN: 0197-016X.
- DT Conference; (Meeting)  
 Conference; Abstract; (Meeting Abstract)
- LA English

ED Entered STN: 14 Jun 2000  
 Last Updated on STN: 5 Jan 2002

CC Neoplasms - General 24002  
 Biochemistry studies - General 10060  
 Pharmacology - General 22002

IT Major Concepts  
 Pharmacology; Tumor Biology

IT Chemicals & Biochemicals  
 ATP: binding affinity; geldanamycin: antineoplastic-drug; **heat shock protein-90**: C-terminus, **chaperone**; **novobiocin**: **heat shock protein-90** inhibitor

IT Methods & Equipment  
 deletion/mutation analysis: detection method

IT Miscellaneous Descriptors  
 Meeting Abstract

RN 56-65-5Q (ATP)  
 42530-29-0Q (ATP)  
 94587-45-8Q (ATP)  
 111839-44-2Q (ATP)  
 30562-34-6 (geldanamycin)  
 303-81-1 (**novobiocin**)

L72 ANSWER 6 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

AN 2000:100786 BIOSIS

DN PREV200000100786

TI **Novobiocin** and related **coumarins** and depletion of **heat shock protein 90**-dependent signaling proteins.

AU Marcu, Monica G.; Schulte, Theodore W.; Neckers, Leonard [Reprint author]

CS National Cancer Institute, 9610 Medical Center Dr., Suite 300, Rockville, MD, 20850, USA

SO Journal of the National Cancer Institute (Bethesda), (Feb. 2, 2000) Vol. 92, No. 3, pp. 242-248. print.  
 CODEN: JNCIEQ. ISSN: 0027-8874.

DT Article

LA English

ED Entered STN: 15 Mar 2000  
 Last Updated on STN: 3 Jan 2002

AB Background: **Heat shock protein 90** (**Hsp90**) interacts with and stabilizes several oncogenic **protein** kinases (e.g., p185erbB2, p60v-src, and Raf-1) and is required for the stability and dominant-negative function of mutated p53 **protein**. Two unrelated antibiotics, geldanamycin and radicicol, bind specifically to an atypical nucleotide-binding pocket of **Hsp90**, a site that shares homology with the adenosine triphosphate (ATP)-binding domain of bacterial DNA gyrase B. This interaction leads to destabilization of **proteins** that interact with **Hsp90**. Since the nucleotide-binding site of gyrase B is targeted by **coumarin** antibiotics (e.g., **novobiocin**), we investigated whether these drugs can also interact with **Hsp90** and affect its activity. Methods: We used immobilized **novobiocin**, geldanamycin, or radicicol to isolate either endogenous **Hsp90** from cell lysates or **Hsp90** deletion fragments translated in vitro. Effects of the **coumarin** antibiotics **novobiocin**, **chlorobiocin**, and **coumermycin A1** on several **proteins** interacting with **Hsp90** were assessed in vitro and in vivo. Results: **Hsp90** binding to immobilized **novobiocin** was competed by soluble **coumarins** and ATP but not by geldanamycin or radicicol. A carboxy-terminal **Hsp90** fragment bound immobilized **novobiocin** but not immobilized geldanamycin, while a geldanamycin-binding amino-terminal fragment did not

bind **novobiocin**. All three **coumarins** markedly reduced cellular levels of p185erbB2, p60v-src, Raf-1, and mutated p53. Furthermore, **novobiocin** reduced Raf-1 levels in the spleens of mice treated with the drug. Conclusions: These **coumarin** antibiotics, particularly **novobiocin**, represent a first-generation alternative to other **Hsp90**-targeting drugs that are not as well tolerated. **Novobiocin**'s unique interaction with **Hsp90** identifies an additional site on this **protein** amenable to pharmacologic interference with small molecules.

CC Pharmacology - General 22002  
 Biochemistry studies - Proteins, peptides and amino acids 10064  
 Biochemistry studies - General 10060

IT Major Concepts  
 Biochemistry and Molecular Biophysics; Pharmacology

IT Chemicals & Biochemicals  
 Raf-1; **chlorobiocin**; **coumermycin A1**; geldanamycin;  
**heat shock protein 90**;  
**novobiocin**; p185-erbB2; p53; p60-v-src; radicicol

ORGN Classifier  
 Muridae 86375  
 Super Taxa  
 Rodentia; Mammalia; Vertebrata; Chordata; Animalia  
 Organism Name  
 mouse  
 Taxa Notes  
 Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals,  
 Rodents, Vertebrates

RN 39868-96-7 (**chlorobiocin**)  
 4434-05-3 (**coumermycin A1**)  
 30562-34-6 (geldanamycin)  
 303-81-1 (**novobiocin**)  
 12772-57-5 (radicicol)

L72 ANSWER 7 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN  
 AN 1999:187460 BIOSIS  
 DN PREV199900187460  
 TI **Novobiocin** and other **coumarin** antibiotics bind to **Hsp90** and cause the degradation of **Hsp90**-dependent signaling proteins.  
 AU Marcu, M. G.; Schulte, T. W.; Neckers, L. M.  
 CS Med. Branch, NCI, Rockville, MD 20850, USA  
 SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 1999) Vol. 40, pp. 724. print.  
 Meeting Info.: 90th Annual Meeting of the American Association for Cancer Research. Philadelphia, Pennsylvania, USA. April 10-14, 1999. American Association for Cancer Research.  
 ISSN: 0197-016X.  
 DT Conference; (Meeting)  
 Conference; Abstract; (Meeting Abstract)  
 LA English  
 ED Entered STN: 5 May 1999  
 Last Updated on STN: 5 May 1999

CC Neoplasms - General 24002  
 Biochemistry studies - General 10060  
 Biophysics - General 10502  
 Enzymes - General and comparative studies: coenzymes 10802  
 Pharmacology - General 22002  
 General biology - Symposia, transactions and proceedings 00520

IT Major Concepts  
 Enzymology (Biochemistry and Molecular Biophysics); Pharmacology; Tumor Biology

IT Diseases  
 cancer: neoplastic disease

Neoplasms (MeSH)  
 IT Chemicals & Biochemicals  
     **novobiocin: coumarin** antibiotic; **Hsp90**  
     inhibitor [**heat shock protein-90**  
     inhibitor]: antineoplastic activity, enzyme inhibitor  
 IT Miscellaneous Descriptors  
     **drug-protein** interaction: biochemical characterization;  
     Meeting Abstract  
 RN 303-81-1 (**novobiocin**)  
     91-64-5 (**COUMARIN**)

=> => fil medline

FILE 'MEDLINE' ENTERED AT 09:37:55 ON 12 AUG 2004

FILE LAST UPDATED: 11 AUG 2004 (20040811/UP). FILE COVERS 1951 TO DATE.

On February 29, 2004, the 2004 MeSH terms were loaded. See HELP RLOAD for details. OLDMEDLINE now back to 1951.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2004 vocabulary. See <http://www.nlm.nih.gov/mesh/> and [http://www.nlm.nih.gov/pubs/techbull/nd03/nd03\\_mesh.html](http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html) for a description of changes.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all tot

L83 ANSWER 1 OF 3 MEDLINE on STN  
 AN 1998324903 MEDLINE  
 DN PubMed ID: 9657982  
 TI Protection from oxidative inactivation of the 20S proteasome by  
     **heat-shock protein 90**.  
 AU Conconi M; Petropoulos I; Emod I; Turlin E; Biville F; Friguet B  
 CS Unite de Biochimie Cellulaire, Institut Pasteur, 28 rue du Dr. Roux, 75724  
     Paris Cedex 15, France.  
 SO Biochemical journal, (1998 Jul 15) 333 ( Pt 2) 407-15.  
     Journal code: 2984726R. ISSN: 0264-6021.  
 CY ENGLAND: United Kingdom  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 199809  
 ED Entered STN: 19980917  
     Last Updated on STN: 20000303  
     Entered Medline: 19980910  
 AB **Heat-shock protein 90 (Hsp**  
     **90)** has been implicated in both protection against oxidative  
     inactivation and inhibition of the multicatalytic proteinase (MCP, also  
     known as 20 S proteasome). We report here that the protective and  
     inhibitory effects of **Hsp 90** depend on the activation  
     state of the proteasome. **Hsp 90** (and also  
     alpha-crystallin) inhibits the N-Cbz-Leu-Leu-Leu-MCA-hydrolysing activity  
     (Cbz=benzyloxycarbonyl; MCA=7-amido-4-methylcoumarin) when the  
     rat liver MCP is in its latent form, but no inhibitory effects are  
     observed when the MCP is in its active form. Metal-catalysed oxidation of  
     the active MCP inactivates the Ala-Ala-Phe-MCA-hydrolysing  
     (chymotrypsin-like), N-Boc-Leu-Ser-Thr-Arg-MCA-hydrolysing (trypsin-like;  
     Boc=t-butyloxycarbonyl), N-Cbz-Leu-Leu-Glu-beta-naphthylamine-hydrolysing  
     (peptidylglutamyl-peptide hydrolase) and N-Cbz-Leu-Leu-Leu-MCA-hydrolysing  
     activities, whereas these activities are actually increased when the MCP



is in its latent form. **Hsp 90** protects against oxidative inactivation of the trypsin-like and N-Cbz-Leu-Leu-Leu-MCA-hydrolysing activities of the MCP active form, and alpha-crystallin protects the trypsin-like activity. The specificity of the **Hsp 90**-mediated protection was assessed by a quantitative analysis of the two-dimensional electrophoretic pattern of MCP subunits before and after oxidation of the MCP, in the presence or absence of **Hsp 90**. Treatment of the FAO hepatoma cell line with iron and ascorbate was found to inactivate the MCP. **Hsp 90** overexpression obtained by challenging the cells with iron was associated with a decreased susceptibility to oxidative inactivation of the MCP trypsin-like activity. Depletion of **Hsp 90** by using antisense oligonucleotides resulted in an increased susceptibility to oxidative inactivation of the MCP trypsin-like activity, providing evidence for the physiological relevance of **Hsp 90**-mediated protection of the MCP.

CT Check Tags: Male; Support, Non-U.S. Gov't

Animals

Ascorbic Acid: ME, metabolism

Catalysis

Cells, Cultured

Crystallins: ME, metabolism

\*Cysteine Endopeptidases: ME, metabolism

Endopeptidases: ME, metabolism

\*Heat-Shock Proteins 90: ME, metabolism

Iron: ME, metabolism

Metals: ME, metabolism

\*Multienzyme Complexes: ME, metabolism

Oligonucleotides, Antisense: ME, metabolism

Oligopeptides: ME, metabolism

Oxidation-Reduction

\*Oxidative Stress

Rats

Rats, Inbred F344

RN 10329-75-6 (leucyl-leucyl-leucine); 50-81-7 (Ascorbic Acid); 7439-89-6 (Iron)

CN 0 (Crystallins); 0 (Heat-Shock Proteins 90); 0 (Metals); 0 (Multienzyme Complexes); 0 (Oligonucleotides, Antisense); 0 (Oligopeptides); EC 3.4.- (Endopeptidases); EC 3.4.22 (Cysteine Endopeptidases); EC 3.4.25.1 (proteasome endopeptidase complex)

L83 ANSWER 2 OF 3 MEDLINE on STN

AN 95257116 MEDLINE

DN PubMed ID: 7738787

TI Thermally-induced cell lysis in Escherichia coli K12.

AU Membrillo-Hernandez J; Nunez-de la Mora A; del Rio-Albrechtsen T; Camacho-Carranza R; Gomez-Eichelmann M C

CS Instituto de Investigaciones Biomedicas, Universidad Nacional Autonoma de Mexico, D.F., Mexico.

SO Journal of basic microbiology, (1995) 35 (1) 41-6.

Journal code: 8503885. ISSN: 0233-111X.

CY GERMANY: Germany, Federal Republic of

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199506

ED Entered STN: 19950615

Last Updated on STN: 19950615

Entered Medline: 19950607

AB Escherichia coli cells exposed to high temperatures exhibit a progressive loss of viability. We observed two mechanisms of cell death induced by lethal temperatures: with and without lysis. The number of cells lysed by heat decreased at later stages of the growth curve, when cells were

pre-treated at lower temperatures for 10 minutes and when cells were pre-treated with **novobiocin**, nalidixic acid and cadmium chloride. Cell lysis was similar in wild type, *rpoH*, *groE* and *dnaK* mutant cells as well as in cells which overproduce **heat shock proteins** GroE or DnaK. Results using cells aligned for cell division and cells growing at 42 degrees C, 45 degrees C and 47 degrees C suggest that cells near division are more sensitive to lysis and that a high concentration of **heat-shock proteins** increases their resistance to lysis.

CT Check Tags: Support, Non-U.S. Gov't

Cadmium: PD, pharmacology

Cadmium Chloride

Cell Division: DE, drug effects

Chlorides: PD, pharmacology

\*Escherichia coli: CY, cytology

Escherichia coli: DE, drug effects

Escherichia coli: GE, genetics

Genes, Bacterial

GroEL Protein: BI, biosynthesis

GroEL Protein: GE, genetics

GroES Protein: BI, biosynthesis

GroES Protein: GE, genetics

Heat

Heat-Shock Proteins 70: BI, biosynthesis

Heat-Shock Proteins 70: GE, genetics

Mutation

Nalidixic Acid: PD, pharmacology

Novobiocin: PD, pharmacology

RN 10108-64-2 (Cadmium Chloride); 303-81-1 (Novobiocin); 389-08-2 (Nalidixic Acid); 7440-43-9 (Cadmium)

CN 0 (Chlorides); 0 (GroEL Protein); 0 (GroES Protein); 0 (Heat-Shock Proteins 70); EC 3.6.1.- (dnaK protein, E coli)

GEN dnaK; groE; rpoH

L83 ANSWER 3 OF 3 MEDLINE on STN

AN 85237507 MEDLINE

DN PubMed ID: 2989538

TI **Novobiocin** blocks the Drosophila heat shock response.

AU Han S; Udvardy A; Schedl P

SO Journal of molecular biology, (1985 May 5) 183 (1) 13-29.

Journal code: 2985088R. ISSN: 0022-2836.

CY ENGLAND: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 198508

ED Entered STN: 19900320

Last Updated on STN: 19900320

Entered Medline: 19850801

AB In the studies reported here we show that the antibiotic **novobiocin**, an in vitro inhibitor of topoisomerase II, blocks the Drosophila heat shock response. If **novobiocin** is added prior to induction, there is no detectable expression of the Drosophila heat shock genes. Moreover, analysis of the chromatin organization of the 87A7 heat shock locus indicates that the antibiotic prevents the structural alterations which normally accompany heat induction. When **novobiocin** is added after induction, transcription appears to be rapidly turned off, and the chromatin organization of the 87A7 locus is "fixed" in an "active" configuration. **Novobiocin** also prevents the re-establishment of the pre-induced 87A7 chromatin organization which occurs during recovery from heat shock. We have also presented data suggesting that this antibiotic blocks transcription at 25 degrees C. These findings raise the possibility that topoisomerase II may be required

in eukaryotes for both gene activation and deactivation.

CT Check Tags: Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.  
 Aspergillus Nuclease S1  
 Autoradiography  
 Chromatin: DE, drug effects  
 Deoxyribonucleases  
 Drosophila: GE, genetics  
 Endonucleases  
 \*Gene Expression Regulation: DE, drug effects  
 Genes: DE, drug effects  
 Heat  
 \*Heat-Shock Proteins: GE, genetics  
 Micrococcal Nuclease  
 Neurospora crassa: EN, enzymology  
 \*Novobiocin: PD, pharmacology  
 RNA, Messenger: BI, biosynthesis

RN 303-81-1 (Novobiocin)

CN 0 (Chromatin); 0 (Heat-Shock Proteins); 0  
 (RNA, Messenger); EC 3.1.- (Deoxyribonucleases); EC 3.1.- (Endonucleases);  
 EC 3.1.30.1 (Aspergillus Nuclease S1); EC 3.1.31.1 (Micrococcal Nuclease)

=> => fil wpix

FILE 'WPIX' ENTERED AT 09:42:50 ON 12 AUG 2004

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 NUMBERS. SEE ALSO:  
<http://www.stn-international.de/archive/stnews/news0104.pdf> <<<

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 SET COST OFF

FILE 'REGISTRY' ENTERED AT 09:01:33 ON 12 AUG 2004

E COUMARIN/CN  
 L1 1 S E3  
 E NOVOBIOCIN/CN  
 L2 1 S E3  
 E CHLOROBIOCIN/CN

L3 1 S E3  
     E HYDROXYCOUMARIN/CN  
 L4 1 S E3  
     E DICUMAROL/CN  
 L5 1 S E3  
     E WARFARIN/CN  
 L6 1 S E3  
     E PHENPROCOUMON/CN  
 L7 1 S E3  
     E COUMERMYCIN/CN  
 L8 1 S E3  
 L9 8 S L1-L8  
     SEL RN  
 L10 213 S E1-E8/CRN  
 L11 130 S L10 NOT (PMS OR IDS OR MXS OR MNS)/CI  
 L12 21 S L11 NOT (COMPD OR WITH OR UNSPECIFIED OR CONJUGATE)  
 L13 192 S L10 NOT L12  
 L14 10774 S COUMARIN OR NOVOBIOCIN OR CHLOROBIOCIN OR HYDROXYCOUMARIN OR  
 L15 10680 S L14 NOT L9,L10

FILE 'HCAPLUS' ENTERED AT 09:05:11 ON 12 AUG 2004

L16 14477 S L9 OR L12  
 L17 219 S L13  
 L18 33774 S L15  
 L19 42695 S ?COUMARIN? OR ?NOVOBIOCIN? OR ?CHLOROBIOCIN? OR ?HYDROXYCOUMA  
 L20 1187 S COUMADIN? OR 2H 1 BENZOPYRAN 2 ONE  
 L21 1146 S DICUMAROL  
 L22 57132 S L16-L21  
     E HEAT SHOCK PROTEIN/CT  
 L23 21562 S HEAT SHOCK(L) PROTEIN  
     E HEAT-SHOCK/CT  
 L24 1699 S E62-E65  
 L25 9914 S E32-E61,E66-E68  
     E E32+ALL  
 L26 15973 S E3-E6,E2+NT  
     E HSP90  
 L27 2401 S E3-E19  
 L28 5 S E34  
 L29 3101 S HSP90 OR HSP 90  
     E CHAPERONE/CT  
     E E4+ALL  
     E E2+ALL  
 L30 6435 S E3,E4,E2+NT  
     E CHAPERONIN/CT  
 L31 2560 S E6-E12  
     E E6+ALL  
 L32 11816 S CHAPERON?  
 L33 90 S L22 AND L23-L32  
 L34 51 S L33 AND (PD<=19990312 OR PRD<=19990312 OR AD<=19990312)  
     E MARCU M/AU  
 L35 65 S E3,E4,E16,E17  
     E MECKERS L/AU  
     E NECKERS L/AU  
 L36 220 S E3-E8  
     E SCHULTE T/AU  
 L37 37 S E3,E7,E9-E13  
 L38 4 S L33 AND L35-L37  
 L39 1 S L34 AND L38  
 L40 4 S L38,L39  
 L41 50 S L34 NOT L40  
 L42 7 S L41 AND (PHARMACEUT? OR PHARMACOL?)/SC,SX  
     SEL DN AN 2 5 6 7 L42  
 L43 4 S L42 AND E1-E12

L44 43 S L41 NOT L42  
 SEL DN AN L44 5 19 30 33 36 37 43  
 L45 7 S L44 AND E13-E33  
 L46 15 S L40,L43,L45 AND L16-L45  
 L47 15 S L46 AND (HSP? OR HEAT SHOCK OR ?PROTEIN? OR 90)  
 L48 3 S L47 AND ?CHAPERON?  
 L49 15 S L47,L48  
 SEL HIT RN

FILE 'REGISTRY' ENTERED AT 09:23:40 ON 12 AUG 2004

L50 7 S E34-E40  
 L51 3 S L50 AND L9,L12  
 L52 4 S L50 AND L13,L15  
 L53 12 S L9,L50-L52

FILE 'REGISTRY' ENTERED AT 09:24:39 ON 12 AUG 2004

FILE 'HCAPLUS' ENTERED AT 09:24:50 ON 12 AUG 2004

FILE 'BIOSIS' ENTERED AT 09:25:17 ON 12 AUG 2004

E MARCU M/AU  
 L54 17 S E3,E9,E10  
 E NECKERS L/AU  
 L55 301 S E3-E11  
 E SCHULTE T/AU  
 L56 69 S E3,E8,E10-E12  
 L57 349 S L54-L56  
 L58 64 S (HSP? OR HEAT SHOCK) AND L57  
 L59 35 S ?CHAPERON? AND L57  
 L60 67 S L58,L59  
 L61 7 S L60 AND L9,L12,L13  
 L62 7 S L60 AND L19  
 L63 0 S L60 AND L20  
 L64 0 S L60 AND L21  
 L65 7 S L61,L62  
 L66 7 S L65 AND ?PROTEIN?  
 L67 7 S L66 AND 90  
 L68 7 S L66-L67

FILE 'BIOSIS' ENTERED AT 09:27:57 ON 12 AUG 2004

L69 7 S L68 AND L54-L68  
 E MARCU M/AU  
 L70 2 S E3,E4 AND L69  
 L71 11 S E3,E4 NOT L70  
 L72 7 S L69,L70

FILE 'MEDLINE' ENTERED AT 09:30:32 ON 12 AUG 2004

L73 12734 S L9,L12,L13  
 L74 27061 S L19,L20,L21  
 L75 27061 S L73,L74  
 E HEAT SHOCK/CT  
 E E13=ALL  
 E HEAT SHOCK/CT  
 E E13+ALL  
 E E2+ALL  
 L76 12992 S E8+NT  
 E E8+ALL  
 L77 38 S L75 AND L76  
 L78 76 S L75 AND (HSP? OR HEAT SHOCK (L) PROTEIN OR ?CHAPERON?)  
 L79 40 S L77,L78 AND PY<=1999  
 L80 2 S L79 AND (HSP90 OR HSP 90 OR 90)  
 L81 1 S L80 AND 90/TI  
 SEL DN AN L79 23 38

L82 2 S E1-E4  
 L83 3 S L81,L82 AND L73-L82

FILE 'MEDLINE' ENTERED AT 09:37:55 ON 12 AUG 2004

FILE 'WPIX' ENTERED AT 09:38:03 ON 12 AUG 2004

E HSP/BI,ABEX  
 L84 146 S E105-E111  
 L85 121 S ((HSP OR HEAT SHOCK PROTEIN) (S) 90) /BIX  
 L86 782 S HEAT SHOCK PROTEIN/BIX  
 L87 381 S ?CHAPERON?/BIX  
 L88 1154 S L84-L87  
 L89 4292 S L19/BIX OR L20/BIX OR L21/BIX  
 E COUMARIN/DCN  
 E E3+ALL  
 L90 331 S E2  
 E NOVOBIOCIN/DCN  
 E E3+ALL  
 L91 65 S E2 OR 1214/DRN  
 L92 39 S E4  
 E CHLOROBIOCIN/DCN  
 E HYDROXYCOUMARIN/DCN  
 E E4+ALL  
 L93 212 S E2 OR 0487/DRN  
 L94 15 S E4  
 L95 51 S E6  
 L96 3 S E8  
 E DICUMAROL/DCN  
 E E3+ALL  
 L97 28 S E2 OR 0264/DRN  
 E WARFARIN/DCN  
 E E3+ALL  
 L98 212 S E2 OR 0487/DRN  
 L99 19 S E4  
 E PHENPROCOUMON/DCN  
 E E3+ALL  
 L100 11 S E2 OR 1253/DRN  
 E COUMERMYCIN/DCN  
 E E4+ALL  
 L101 12 S E2  
 L102 10 S L88 AND L89-L101

FILE 'WPIX' ENTERED AT 09:42:50 ON 12 AUG 2004

=> d all l102 ab tech abex tot

L102 ANSWER 1 OF 10 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN  
 AN 2004-506948 [48] WPIX  
 DNN N2004-400584 DNC C2004-187639  
 TI Radially expandable modular stent useful in the treatment of restenosis  
 includes two stent modules forming two passageways; and polymer bridge  
 between the stent modules such that both passageways are in fluid  
 communication.  
 DC A96 B05 B07 D22 P32  
 IN KANTOR, J  
 PA (MEDT) MEDTRONIC VASCULAR  
 CYC 98  
 PI WO 2004052237 A2 20040624 (200448)\* EN 26 A61F000-00  
 RW: AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO  
 SE SI SK TR  
 W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK  
 DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR  
 KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT

RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM  
ZW

ADT WO 2004052237 A2 WO 2003-US39290 20031209

PRAI US 2002-432278P 20021209

IC ICM A61F000-00

AB WO2004052237 A UPAB: 20040728

NOVELTY - A radially expandable modular stent (A1) includes a first stent module (F1) forming a first passageway; at least a second stent module (S1) forming at least a second passageway; and at least one polymer bridge (P1) in communication with (F1) and (S1). (P1) Couples (F1) to (S1) such that both passageways are in fluid communication.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for manufacturing (M1) of (A1) involving forming (F1) and (S1) from at least one stent material, and coupling (S1) to (F1) with (P1).

ACTIVITY - Vasotropic.

MECHANISM OF ACTION - None given.

USE - In vascular devices for implantation within the body of patients (claimed) during the treatment of restenosis.

ADVANTAGE - The polymeric coating containing therapeutic drugs provides controlled release of the drug in the localized environment, and contributes to great versatility of the vascular devices. The modular stents provide radially expanding force or support to a luminal structure; exhibit improved flexibility; and have decreased potential to module compaction.

Dwg.0/10

FS CPI GMPI

FA AB; DCN

MC CPI: A12-V02; A12-V03; B01-A01; B01-A02; B04-C01; B04-C01A; B04-C01B; B04-C02A; B04-C02B; B04-C02E; B04-C02E1; B04-C03; B04-H06; B04-H06B; B04-H06F; B04-H06J; B04-N04; B05-A03B; B05-C03; B06-A01; B06-A03; B06-D09; B06-E03; B06-E05; B07-D12; B08-C01; B10-A10; B10-A15; B10-C03; B10-C04D; B10-D01; B14-F01G; D09-C01; D09-C04

AB WO2004052237 A UPAB: 20040728

NOVELTY - A radially expandable modular stent (A1) includes a first stent module (F1) forming a first passageway; at least a second stent module (S1) forming at least a second passageway; and at least one polymer bridge (P1) in communication with (F1) and (S1). (P1) Couples (F1) to (S1) such that both passageways are in fluid communication.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for manufacturing (M1) of (A1) involving forming (F1) and (S1) from at least one stent material, and coupling (S1) to (F1) with (P1).

ACTIVITY - Vasotropic.

MECHANISM OF ACTION - None given.

USE - In vascular devices for implantation within the body of patients (claimed) during the treatment of restenosis.

ADVANTAGE - The polymeric coating containing therapeutic drugs provides controlled release of the drug in the localized environment, and contributes to great versatility of the vascular devices. The modular stents provide radially expanding force or support to a luminal structure; exhibit improved flexibility; and have decreased potential to module compaction.

Dwg.0/10

TECH UPTX: 20040728

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Component: At least one of (F1), (S1), and (P1) includes at least one therapeutic agent selected from anti-thrombotic agent, platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-beta), heparin, anti-inflammatory agent, anti-proliferation agent, rapamycin, angiopeptin, methotrexate, paclitaxel, anti-microbial agent, anti-metabolic agent, anti-platelet agent, anti-coagulant agent, Nitric Oxide releasing agent, chaperone inhibitor, benzoquinone ansamycins (e.g. geldanamycin, herbimycin and macbecin), glitazone, matrix metalloproteinase inhibitor (MMPI), antisense polynucleotide, transforming nucleotide, epothilones,

aspirin, coumadin, D-phenylalanyl-prolyl-arginine chloromethylketone (PPACK), hirudin, polypeptide from angiostatin and endostatin, 5-fluorouracil, estradiol, P-selectin glycoprotein ligand-1 chimera, abciximab, exochelin, eleutherobin and sarcodictyin, fludarabine, sirolimus, ABT-578, certican, Sulindac, tranilast, thiazolidiones (e.g. rosiglitazone, troglitazone, pioglitazone, darglitazone and englitazone), tetracycline, VEGF, insulin-like growth factor (IGF), fibroblast growth factor (FGF), Arg-Gly-Asp peptide, estrogen (e.g. 17 betaeta-estradiol), beta or gamma ray emitter (radioactive) agents, vasodilators (e.g. nitric oxide), various making agents (e.g. radio-opaque and/or echogenic materials).

Preferred Method: (M1) Further involves coating surfaces of (F1) and (S1) with the polymer material to form (P1), particularly applying the polymer material to (S1) and (F1) at a location where they contact each other.

(P1) Is applied by dipping, spraying, and/or vapor deposition. (M1) further involves applying at least one therapeutic agent to at least one of (F1), (S1) and (P1).

TECHNOLOGY FOCUS - INORGANIC CHEMISTRY - Preferred Component: At least one of (F1) and (S1) is manufactured from at least one material selected from stainless steel, tantalum, titanium, Nickel-Titanium alloy, shape memory alloy, super elastic alloy, low-modulus Ti-Nb-Zr alloy, and cobalt-nickel alloy steel (MP-35N). (F1) And (S1) are porous or non-porous.

TECHNOLOGY FOCUS - POLYMERS - Preferred Device: (P1) Comprises a polymer material applied to at least one surface of (F1) and (S1). (P1) Is applied to (S1) at a point of contact with (F1). (P1) Further comprises a polymer hinge that forms a gap between (F1) and (S1); and a polymer weld coupling (S1) to (F1) so that (S1) is in contact with (F1).

Preferred Components: (P1) Is manufactured from a biocompatible and biodegradable polymer selected from poly(L-lactic acid), polycaprolactone, poly(lactide-co-glycolide), poly(ethylene-vinyl acetate), poly(hydroxybutyrate-co-valerate), polydioxanone, polyorthoester, polyanhydride, poly(glycolic acid), poly(D,L-lactic acid), poly(glycolic acid-co-trimethylene carbonate), polyphosphoester, polyphosphoester urethane, poly(amino acids), cyanoacrylate, poly(trimethylene carbonate), poly(iminocarbonate), copoly(ether-ester), polyalkylene oxalate, polyphosphazene, biomolecule, fibrin, fibrinogen, cellulose, starch, collagen, hyaluronic acid, polyurethane, silicone, polyester, polyolefin, polyisobutylene, ethylene-alpha-olefin copolymer, acrylic polymer, acrylic copolymer, ethylene-co-vinylacetate, polybutylmethacrylate, vinyl halide polymer, vinyl halide copolymer, polyvinyl chloride, polyvinyl ether, polyvinyl methyl ether, polyvinylidene halide, polyvinylidene fluoride, polyvinylidene chloride, polyacrylonitrile, polyvinyl ketone, polyvinyl aromatic, polystyrene, polyvinyl ester, polyvinyl acetate, copolymer of vinyl monomer, ethylene-methyl methacrylate copolymer, acrylonitrile-styrene copolymer, ABS resin, ethylene-vinyl acetate copolymer, polyamide, Nylon 66, polycaprolactam, alkyl resin, polycarbonate, polyoxymethylene, polyimide, polyether, epoxy resin, polyurethane, rayon, rayon-triacetate, cellulose acetate/butyrate, cellophane, cellulose nitrate, cellulose propionate, cellulose ether, and carboxymethyl cellulose. At least one of (F1) and (S1) is manufactured from biocompatible polymers or biocompatible elastomer.

L102 ANSWER 2 OF 10 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2003-898528 [82] WPIX

DNC C2003-255363

TI New vaccine capable of modulating the immune system, useful for preventing or treating viral, bacterial or parasitic infections.

DC B04 B05 D16

IN BONAGURA, V R; DEVOTI, J; LANCE, H W; MAYHALL, J M; DEVOTI, J R

PA (BONA-I) BONAGURA V R; (DEVO-I) DEVOTI J; (LANC-I) LANCE H W; (MAYH-I) MAYHALL J M; (OMEG-N) OMEGA PHARM INC



CYC 102

PI US 2003175777 A1 20030918 (200382)\* 52 A61K039-295  
 WO 2003074000 A2 20030912 (200382) EN A61K000-00  
 RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS  
 LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW  
 W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK  
 DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR  
 KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT  
 RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM  
 ZW

AU 2003217877 A1 20030916 (200430) A61K039-295

ADT US 2003175777 A1 Provisional US 2002-354397P 20020204, Provisional US  
 2002-360788P 20020301, US 2003-357913 20030204; WO 2003074000 A2 WO  
 2003-US6430 20030303; AU 2003217877 A1 AU 2003-217877 20030303

FDT AU 2003217877 A1 Based on WO 2003074000

PRAI US 2003-357913 20030204; US 2002-354397P 20020204;  
 US 2002-360788P 20020301

IC ICM A61K000-00; A61K039-295

ICS A01N043-04; A61K031-70; A61K039-116; C12Q001-68

AB US2003175777 A UPAB: 20031223

NOVELTY - A vaccine capable of modulating the immune system of a subject comprising a compound consisting of eleutheroside, coniferylaldehyde, caffeic acid ethyl ester, chlorogenic acid, sinapinalcohol, isofraxidin, syringaresinol or 6,8-dimethoxy-7-hydroxycoumarin, is new. The eleutheroside comprises a compound consisting of eleutheroside A, B, C, D, E, F or G.

ACTIVITY - Virucide; Antibacterial; Antiparasitic.

No biological data given.

MECHANISM OF ACTION - Vaccine.

USE - The vaccine is useful for modulating the immune system for preventing or treating viral, bacterial or parasitic infections (claimed).  
 Dwg.0/1

FS CPI

FA AB; DCN

MC CPI: B06-A01; B06-A02; B07-A02B; B10-C03; B10-D01; B14-A01; B14-A02;  
 B14-B02; B14-S11; D05-H07

AB US2003175777 A UPAB: 20031223

NOVELTY - A vaccine capable of modulating the immune system of a subject comprising a compound consisting of eleutheroside, coniferylaldehyde, caffeic acid ethyl ester, chlorogenic acid, sinapinalcohol, isofraxidin, syringaresinol or 6,8-dimethoxy-7-hydroxycoumarin, is new. The eleutheroside comprises a compound consisting of eleutheroside A, B, C, D, E, F or G.

ACTIVITY - Virucide; Antibacterial; Antiparasitic.

No biological data given.

MECHANISM OF ACTION - Vaccine.

USE - The vaccine is useful for modulating the immune system for preventing or treating viral, bacterial or parasitic infections (claimed).  
 Dwg.0/1

TECH UPTX: 20031223

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Vaccine: The vaccine is capable of modulating the immune system of a subject. The modulation prevents or treats viral infections caused by e.g. HIV, hepatitis A, B, C or D virus, Dengue virus or Respiratory Syncytial virus, bacterial infections caused by e.g. Mycobacterium, Bacillus, Hemophilus, Pneumococcus or Streptococcus species, or parasitic infections caused by e.g. Plasmodium, Schistosoma or Leishmania species. The vaccine increases or decreases the expression of the protein, comprising interleukin (IL)-10, heat shock protein (HSP)-70b, HSP-70-2, HSP-40, HSP-90, heat shock transcription factor-4, c-Fos, junB, ATF-3, tumor necrosis factor (TNF)-alpha, human lymphoid transcription factor, CD14 differentiation antigen, Lck, platelet derived endothelial growth factor,

CCR2, CCR2a, CCR5 or CCR6.

ABEX UPTX: 20031223

ADMINISTRATION - The composition is administered via oral or parenteral route. No dosage given.

EXAMPLE - No relevant examples given.

L102 ANSWER 3 OF 10 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2003-229528 [22] WPIX

DNC C2003-059073

TI Synthesis and function inhibitors for **heat shock proteins** comprise vitamin K analog or **coumarin** anticoagulant derivatives.

DC B05

IN KAI, H

PA (KAIH-I) KAI H; (YAMA-I) YAMATSU T; (YAMA-I) YAMATSU I

CYC 100

PI WO 2003007927 A1 20030130 (200322)\* JA 34 A61K031-122

RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU  
MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK  
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS KE KG KP KR KZ  
LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO  
RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW

JP 2003089636 A 20030328 (200331) 11 A61K031-122

ADT WO 2003007927 A1 WO 2002-JP6796 20020704; JP 2003089636 A JP 2002-8258  
20020117

PRAI JP 2002-8258 20020117; JP 2001-212354 20010712

IC ICM A61K031-122

ICS A61K031-352; A61K031-37; A61P017-02; A61P025-28; A61P035-00;  
A61P043-00

ICA C07D311-56

AB WO2003007927 A UPAB: 20030402

NOVELTY - Synthesis and function inhibitors for **heat shock proteins** comprise a vitamin K analog or derivative or a **coumarin** anticoagulant or its derivative.

ACTIVITY - Cytostatic; Neuroprotective.

In assays using nude mice implanted with A549 cells administration of vitamin K2 at 50 mg/kg intraabdominally reduced tumor volume after 1 week compared to an increase in tumor volume in the control.

MECHANISM OF ACTION - HSP-Antagonist.

USE - As synthesis and function inhibitors for **heat shock proteins** for treating and preventing cancer and multiple sclerosis.

Dwg.0/10

FS CPI

FA AB; DCN

MC CPI: B04-N04; B14-F04

AB WO2003007927 A UPAB: 20030402

NOVELTY - Synthesis and function inhibitors for **heat shock proteins** comprise a vitamin K analog or derivative or a **coumarin** anticoagulant or its derivative.

ACTIVITY - Cytostatic; Neuroprotective.

In assays using nude mice implanted with A549 cells administration of vitamin K2 at 50 mg/kg intraabdominally reduced tumor volume after 1 week compared to an increase in tumor volume in the control.

MECHANISM OF ACTION - HSP-Antagonist.

USE - As synthesis and function inhibitors for **heat shock proteins** for treating and preventing cancer and multiple sclerosis.

Dwg.0/10

TECH UPTX: 20030402

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Components: **Heat**

**shock protein** has a molecular weight of 40-73 kD and **coumarin** anticoagulant or its derivative is **warfarin** or **dicumarol** or their salts.

ABEX UPTX: 20030402

ADMINISTRATION - Dosage is 0.01-50 (preferably 0.2-10) mg/kg orally or 0.002-10 (preferably 0.04-2) mg/kg parenterally.

L102 ANSWER 4 OF 10 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2003-140320 [13] WPIX

DNN N2003-111531 DNC C2003-035542

TI Use of a compound that e.g. inhibits **heat shock protein 90**, for treating disease associated with protein aggregation and amyloid formation e.g. polyglutamine expansion or Creutzfeld Jakob disease.

DC B05 S03

IN HARTL, U; SITTler, A; WANKER, E

PA (PLAC) MAX PLANCK GES FOERDERUNG WISSENSCHAFTEN

CYC 101

PI WO 2002094259 A1 20021128 (200313)\* EN 23 A61K031-395

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ  
NL OA PT SD SE SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK  
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR  
KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT  
RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM  
ZW

EP 1387678 A1 20040211 (200411) EN A61K031-395

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT  
RO SE SI TR

ADT WO 2002094259 A1 WO 2002-EP4893 20020503; EP 1387678 A1 EP 2002-740561  
20020503, WO 2002-EP4893 20020503

FDT EP 1387678 A1 Based on WO 2002094259

PRAI US 2001-288718P 20010504; EP 2001-110769 20010503

IC ICM A61K031-395

ICS A61K031-365; A61P025-28; G01N033-566

AB WO 200294259 A UPAB: 20030224

NOVELTY - Use of a compound(s) that inhibit **heat shock protein (Hsp) 90**, binding to HSF1 to **Hsp90** or that activate expression of both Hsp40 and Hsp70 for treating or preventing disease associated with protein aggregation and amyloid formation.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) Designing a drug for the treatment of disease associated with protein aggregation and amyloid formation involving:

(a) identifying the sites of compound that binds Hsp40 and/or 70 or identifying sites of a compound that binds to **Hsp 90** or to HSF-1 and/or their homologues or other components participating in the regulation of the stress protein response,

(b) molecular modeling of both the binding sites in the compound and the Hsp, and

(c) modifying the compound to improve its binding specificity for the Hsp or HSF-1;

(2) Identifying an activator of the expression of Hsp40 and/or 70 involving testing small molecules or peptides for the activation of translation, or testing a compound for the activation of transcription. The compound binds to the promoter region of the genes encoding the Hsp and preferably with transcription factors and their responsive elements;

(3) Identifying an inhibitor of **Hsp90** involving testing a compound selected from small molecules or peptides for inhibition of **Hsp90** ATPase activity function, and selecting a compound that tests positive;

(4) Identifying an inhibitor of binding of HSF-1 to **Hsp90**

involving testing a compound for inhibition of binding of HSF-1 to **Hsp90**, and selecting a compound that tests positive.

ACTIVITY - Neuroprotective; Nootropic; Anticonvulsant; Antidiabetic; Antiparkinsonian.

MECHANISM OF ACTION - **Hsp 90** inhibitor; Inhibitor of binding to HSF1 to **Hsp90**; Activator of expression of both **Hsp40** and **Hsp70**.

In order to induce a heat shock response COS-1 cells expressing the fusion of enhanced green fluorescent protein (EGFP) and the huntingtin exon 1 protein with 72 glutamines (HD72Q) were treated with various concentrations of geldamycin (GA). Forty hours post transfection, total cell extracts were prepared and expression of EGFP-HD72Q protein migrating in the SDS-gel at approx. 57 kDa was detected in protein extracts of untransfected control cells. Treatment of cells with increasing concentration of GA (18-360 nM) had no effect on EGFP-HD72Q expression. In contrast, the expression of each of the molecular **chaperones Hsp-40, Hsp-70 and Hsp-90** increased with increasing GA-concentrations, indicating that treatment of cells with GA triggers heat shock response. Addition of GA to final concentration of 360 nM resulted in 3-4 fold up-regulation of **Hsp40, Hsp70 and Hsp90** compared to the untreated control.

USE - The compounds are used for treating or preventing disease associated with protein aggregation and amyloid formation such as polyglutamine expansion; for treating Creutzfeldt Jakob disease, Huntington's disease, spinal and bulbar muscular atrophy, dentatorubral pallidoluysian atrophy, spinocerebellar ataxia type 1, 2, 3, 6 or 7, Alzheimer disease, primary systemic amyloidosis, secondary systemic amyloidosis, senile systemic amyloidosis, familial amyloid polyneuropathy I, hereditary cerebral amyloid angiopathy, hemodialysis-related amyloidosis, familial amyloid polyneuropathy III, Finnish hereditary systemic amyloidosis, type II diabetes, medullary carcinoma of the thyroid, spongiform encephalopathies: Kuru, Gerstmann-Straussler-Scheinker syndrome (GSS), familial insomnia, scrapie, atrial amyloidosis, hereditary non-neuropathic systemic amyloidosis, injection-localized amyloidosis, hereditary renal amyloidosis and Parkinson's disease.

ADVANTAGE - The compound modifies site of action, spectrum of activity, improves organ specificity and potency. It also decreases toxicity and side effects, whilst modifying onset of therapeutic action, duration of effect, pharmacokinetic parameters (resorption, distribution, metabolism and excretion), and physico-chemical parameters (solubility, hygroscopicity, color, taste, odor, stability, state).

Dwg.0/6

FS CPI EPI

FA AB; DCN

MC CPI: B04-C01; B04-E01; B04-H01; B04-L01; B04-N04; B06-H; B11-C08E; B11-C08F3; B11-C08F4; B12-K04E; B14-J01A3; B14-J01A4; B14-J01B4; B14-N10; B14-N11; B14-N16; B14-S04

EPI: S03-E14H4

AB WO 200294259 A UPAB: 20030224

NOVELTY - Use of a compound(s) that inhibit **heat shock protein (Hsp) 90**, binding to HSF1 to **Hsp90** or that activate expression of both **Hsp40** and **Hsp70** for treating or preventing disease associated with protein aggregation and amyloid formation.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) Designing a drug for the treatment of disease associated with protein aggregation and amyloid formation involving:

(a) identifying the sites of compound that binds **Hsp40** and/or **70** or identifying sites of a compound that binds to **Hsp 90** or to HSF-1 and/or their homologues or other components participating in the regulation of the stress protein response,

(b) molecular modeling of both the binding sites in the compound and

the Hsp, and

(c) modifying the compound to improve its binding specificity for the Hsp or HSF-1;

(2) Identifying an activator of the expression of Hsp40 and/or 70 involving testing small molecules or peptides for the activation of translation, or testing a compound for the activation of transcription. The compound binds to the promoter region of the genes encoding the Hsp and preferably with transcription factors and their responsive elements;

(3) Identifying an inhibitor of Hsp90 involving testing a compound selected from small molecules or peptides for inhibition of Hsp90 ATPase activity function, and selecting a compound that tests positive;

(4) Identifying an inhibitor of binding of HSF-1 to Hsp90 involving testing a compound for inhibition of binding of HSF-1 to Hsp90, and selecting a compound that tests positive.

ACTIVITY - Neuroprotective; Nootropic; Anticonvulsant; Antidiabetic; Antiparkinsonian.

MECHANISM OF ACTION - Hsp 90 inhibitor; Inhibitor of binding to HSF1 to Hsp90; Activator of expression of both Hsp40 and Hsp70.

In order to induce a heat shock response COS-1 cells expressing the fusion of enhanced green fluorescent protein (EGFP) and the huntingtin exon 1 protein with 72 glutamines (HD72Q) were treated with various concentrations of geldamycin (GA). Forty hours post transfection, total cell extracts were prepared and expression of EGFP-HD72Q protein migrating in the SDS-gel at approx. 57 kDa was detected in protein extracts of untransfected control cells. Treatment of cells with increasing concentration of GA (18-360 nM) had no effect on EGFP-HD72Q expression. In contrast, the expression of each of the molecular chaperones Hsp-40, Hsp-70 and Hsp-90 increased with increasing GA-concentrations, indicating that treatment of cells with GA triggers heat shock response. Addition of GA to final concentration of 360 nM resulted in 3-4 fold up-regulation of Hsp40, Hsp70 and Hsp90 compared to the untreated control.

USE - The compounds are used for treating or preventing disease associated with protein aggregation and amyloid formation such as polyglutamine expansion; for treating Creutzfeldt Jakob disease, Huntington's disease, spinal and bulbar muscular atrophy, dentatorubral pallidoluysian atrophy, spinocerebellar ataxia type 1, 2, 3, 6 or 7, Alzheimer disease, primary systemic amyloidosis, secondary systemic amyloidosis, senile systemic amyloidosis, familial amyloid polyneuropathy I, hereditary cerebral amyloid angiopathy, hemodialysis-related amyloidosis, familial amyloid polyneuropathy III, Finnish hereditary systemic amyloidosis, type II diabetes, medullary carcinoma of the thyroid, spongiform encephalopathies: Kuru, Gerstmann-Straussler-Scheinker syndrome (GSS), familial insomnia, scrapie, atrial amyloidosis, hereditary non-neuropathic systemic amyloidosis, injection-localized amyloidosis, hereditary renal amyloidosis and Parkinson's disease.

ADVANTAGE - The compound modifies site of action, spectrum of activity, improves organ specificity and potency. It also decreases toxicity and side effects, whilst modifying onset of therapeutic action, duration of effect, pharmacokinetic parameters (resorption, distribution, metabolism and excretion), and physico-chemical parameters (solubility, hygroscopicity, color, taste, odor, stability, state).

Dwg.0/6

TECH

UPTX: 20030224

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Method: Identification is effected by site-directed mutagenesis and/or chimeric protein studies. The compound is derived from geldamycin by modeling geldamycin by peptidomimetic and chemically synthesizing the modeled compound. The compound can also be obtained by screening at least partially randomized peptide library and/or chemical compounds library for the compound. The modification is achieved by either:

(1) Esterification of carboxyl groups;  
 (2) Esterification of hydroxyl groups with carbon acids;  
 (3) Esterification of hydroxyl groups to, e.g. phosphates, pyrophosphates or sulfates or hemi succinates;  
 (4) Formation of salts or complexes;  
 (5) Synthesis of pharmacologically active polymers;  
 (6) Introduction of hydrophilic moieties;  
 (7) Introduction/exchange of substituents on aromates or side chains, change of substituent pattern;  
 (8) Modification by introduction of isosteric or bioisosteric moieties;  
 (9) Synthesis of homologous compounds;  
 (10) Introduction of branched side chains;  
 (11) Conversion of alkyl substituents to cyclic analogues;  
 (12) Derivatization of hydroxyl group to ketals, acetals;  
 (13) N-acetylation to amides, phenylcarbamates;  
 (14) Synthesis of Mannich bases, imines; and/or  
 (15) Transformation of ketones or aldehydes to Schiff's bases, oximes, acetals, ketals, enolesters, oxazolidines, thiozolidines.  
 Inhibition or activation of the **heat shock protein** is assayed by Reporter assays, immunofluorescence microscopy, a filter retardation assay or ATPase assays.

TECHNOLOGY FOCUS - BIOLOGY - Preferred Protein: The Hsp is human **heat shock protein**. The Hsp40 is Hdj-1 or Hdj-2.

ABEX UPTX: 20030224

SPECIFIC COMPOUNDS - The use of Geldanamycin, Radicicol, Herbimycin A, **Novobiocin**, 17-allylamino-17-demethoxygeldanamycin and macbecin are specifically claimed as the compound.

ADMINISTRATION - The compound is administered intravenously, intraperitoneally, subcutaneously, intramuscularly, topically, intradermally, intranasally or intrabronchially. The dosage is 0.001-1000 microg or 1 microg -10 mg units/per kg body weight per minutes for continuous infusion.

L102 ANSWER 5 OF 10 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2002-147972 [19] WPIX

DNC C2002-045967

TI Use of collagen promoter such as geldanamycin, for treating fibrogaic disorder.

DC B02

IN STREHLOW, D

PA (UYBO-N) UNIV BOSTON; (STRE-I) STREHLOW D

CYC 95

PI WO 2002002123 A1 20020110 (200219)\* EN 51 A61K031-66

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ  
 NL OA PT SD SE SL SZ TR TZ UG ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK  
 DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ  
 LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD  
 SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2001071567 A 20020114 (200237) A61K031-66

US 2004082498 A1 20040429 (200429) A61K031-00

ADT WO 2002002123 A1 WO 2001-US20578 20010628; AU 2001071567 A AU 2001-71567  
 20010628; US 2004082498 A1 WO 2001-US20578 20010628, US 2002-312287  
 20021220

FDT AU 2001071567 A Based on WO 2002002123

PRAI US 2000-214950P 20000629; US 2002-312287 20021220

IC ICM A61K031-00; A61K031-66

ICS A61K031-70; A61K039-395

AB WO 200202123 A UPAB: 20020321

NOVELTY - A composition (A) comprises an inhibitor of a collagen promoter

(preferably an inhibitor of **heat shock protein 90 alpha (Hsp 90) chaperone** function) and an inert carrier vehicle for topical application.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for an article comprising a packaging material and (A). The packaging material also comprises a label with instructions for use.

ACTIVITY - Dermatological; Immunosuppressive; Antirheumatic; Antarthritic; Hepatoprotic; Anti-inflammatory; Ophthalmological.  
No biological data given.

MECHANISM OF ACTION - Collagen promoter inhibitor (preferably **Hsp 90 chaperone** inhibitor); TGF- beta signal transduction blocker; Smad-controlled promoter activation inhibitor.

USE - For prophylaxis or treatment of a fibrogenic disorder e.g. scleroderma, polymyositis, systemic lupus erythematosus, rheumatoid arthritis, keloid formulation, formulation, interstitial nephritis and pulmonary fibrosis or liver cirrhosis (all claimed).

ADVANTAGE - The composition does not detectably affect steroid hormone receptor activity; decreases Smad DNA binding and has no effect on the PN1 promoter.

Dwg.0/11

FS

CPI

FA

AB; DCN

MC

CPI: B02-Z; B06-H; B14-C09B; B14-G02D; B14-K01; B14-N10; B14-N12

AB

WO 200202123 A UPAB: 20020321

NOVELTY - A composition (A) comprises an inhibitor of a collagen promoter (preferably an inhibitor of **heat shock protein 90 alpha (Hsp 90) chaperone** function) and an inert carrier vehicle for topical application.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for an article comprising a packaging material and (A). The packaging material also comprises a label with instructions for use.

ACTIVITY - Dermatological; Immunosuppressive; Antirheumatic; Antarthritic; Hepatoprotic; Anti-inflammatory; Ophthalmological.  
No biological data given.

MECHANISM OF ACTION - Collagen promoter inhibitor (preferably **Hsp 90 chaperone** inhibitor); TGF- beta signal transduction blocker; Smad-controlled promoter activation inhibitor.

USE - For prophylaxis or treatment of a fibrogenic disorder e.g. scleroderma, polymyositis, systemic lupus erythematosus, rheumatoid arthritis, keloid formulation, formulation, interstitial nephritis and pulmonary fibrosis or liver cirrhosis (all claimed).

ADVANTAGE - The composition does not detectably affect steroid hormone receptor activity; decreases Smad DNA binding and has no effect on the PN1 promoter.

Dwg.0/11

TECH

UPTX: 20020321

TECHNOLOGY FOCUS - BIOLOGY - Preferred Components: Geldanamycin, macbecin I and II, herbimycin, radicicol and **novobiocin** are claimed as the inhibitor of **Hsp 90-chaperone** function.

ABEX

UPTX: 20020321

ADMINISTRATION - The composition is administered locally (preferably topically), orally or parenterally (including intranasally, subcutaneously, intramuscularly, intravenously or intra-arterially) in dosage of 0.05 - 10 (preferably 0.25 - 2.5) microg/kg/day. For a 70 kg human patient the dosage is 50 mug/day.

EXAMPLE - None given.

L102 ANSWER 6 OF 10 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2001-542488 [61] WPIX

DNC C2001-162030

TI

Medicament for inducing tolerance to antigens, e.g. those causing autoimmune disease, allergy or infections, containing the antigen together with steroid sulfatase inhibitor as adjuvant to improve tolerance

induction.

DC B04 B05 D16

IN WICKENS, T

PA (BION-N) BIONETWORKS GMBH

CYC 1

PI DE 10005643 A1 20010816 (200161)\* 9 A61K039-39

ADT DE 10005643 A1 DE 2000-10005643 20000209

PRAI DE 2000-10005643 20000209

IC ICM A61K039-39

AB DE 10005643 A UPAB: 20011024

NOVELTY - A medicament (A) contains as active component a combination of a steroid sulfatase (SS) inhibitor (I) and an antigen (II).

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for a composition comprising (I) and (II).

ACTIVITY - Immunosuppressive; antiallergic; antirheumatic; antiarthritic; neuroprotective; ophthalmological; antiinflammatory; antidiabetic; dermatological; antibacterial; virucidal; antifungal; antitubercular.

In tolerance tests involving experimental autoimmune encephalitis in rats (an animal model of multiple sclerosis), administration of SS inhibitors (e.g. 1-8 mg of estrone-3-O-sulfamate (Ia) in oil, subcutaneously) before sensitization markedly reduced the amount of antigen (i.e. MBP or MOG) required to produce tolerance (no quantitative results given).

MECHANISM OF ACTION - Steroid sulfatase inhibitor; vaccine.

USE - (A) is used for induction of tolerance (especially mucosal tolerance) (claimed). The claims also cover the use of (I) in combination with (II) for induction of tolerance; and a method for inducing tolerance in the control of autoimmune diseases, allergies, transplant rejection and graft-versus-host-disease in humans or other mammals, involving administration of (I) in combination with the administration of (II) (or a nucleic acid encoding (II)). (II) include antigens associated with rheumatoid arthritis, multiple sclerosis, uveitis, type I diabetes, lupus erythematosus or infectious diseases; benzoyl penicillin, insulin, ovalbumin or lactalbumin; and components of pollen, foods or house dust mites (all claimed). Infection-associated (II) include bacterial, viral or fungal antigens, such as influenza, leishmania, cytomegalovirus, pneumonia, Streptococcus B, Chlamydia, Helicobacteria, hepatitis C, human papilloma virus or Mycobacterium tuberculosis antigens.

ADVANTAGE - Combining (I) (as adjuvant) with (II) improves and optimizes the induction of tolerance to a wide range of (II). In particular the combination of (I) and (II) provides an effective, well tolerated oral vaccine.

Dwg.0/0

FS CPI

FA AB; DCN

MC CPI: B01-A01; B02-P; B04-C02; B04-C02V; B04-D01; B04-E01; B04-E02A; B04-E03A; B04-E06; B04-F01; B04-F10; B04-F10B4; B04-F11; B04-J03A; B04-N02; B04-N04; B04-N06; B06-A01; B10-A08; B14-A01; B14-A01B1; B14-A01B2; B14-A02; B14-A02A3; B14-A02A6; B14-A02B2; B14-A03; B14-A04; B14-C09B; B14-G02A; B14-G02C; B14-G02D; B14-N03; B14-N12; B14-N17; B14-S01; B14-S04; B14-S11; D05-H07; D05-H12A; D05-H12D2; D05-H17A6

AB DE 10005643 A UPAB: 20011024

NOVELTY - A medicament (A) contains as active component a combination of a steroid sulfatase (SS) inhibitor (I) and an antigen (II).

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for a composition comprising (I) and (II).

ACTIVITY - Immunosuppressive; antiallergic; antirheumatic; antiarthritic; neuroprotective; ophthalmological; antiinflammatory; antidiabetic; dermatological; antibacterial; virucidal; antifungal; antitubercular.

In tolerance tests involving experimental autoimmune encephalitis in



rats (an animal model of multiple sclerosis), administration of SS inhibitors (e.g. 1-8 mg of estrone-3-O-sulfamate (Ia) in oil, subcutaneously) before sensitization markedly reduced the amount of antigen (i.e. MBP or MOG) required to produce tolerance (no quantitative results given).

MECHANISM OF ACTION - Steroid sulfatase inhibitor; vaccine.

USE - (A) is used for induction of tolerance (especially mucosal tolerance) (claimed). The claims also cover the use of (I) in combination with (II) for induction of tolerance; and a method for inducing tolerance in the control of autoimmune diseases, allergies, transplant rejection and graft-versus-host-disease in humans or other mammals, involving administration of (I) in combination with the administration of (II) (or a nucleic acid encoding (II)). (II) include antigens associated with rheumatoid arthritis, multiple sclerosis, uveitis, type I diabetes, lupus erythematosus or infectious diseases; benzoyl penicillin, insulin, ovalbumin or lactalbumin; and components of pollen, foods or house dust mites (all claimed). Infection-associated (II) include bacterial, viral or fungal antigens, such as influenza, leishmania, cytomegalovirus, pneumonia, Streptococcus B, Chlamydia, Helicobacteria, hepatitis C, human papilloma virus or Mycobacterium tuberculosis antigens.

ADVANTAGE - Combining (I) (as adjuvant) with (II) improves and optimizes the induction of tolerance to a wide range of (II). In particular the combination of (I) and (II) provides an effective, well tolerated oral vaccine.

Dwg.0/0

TECH

UPTX: 20011024

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred SS Inhibitors: (I) are selected from endogenous or exogenous SS inhibitors and antisense nucleic acids, including specific inhibitors for one or more SS isoenzymes. (I) is especially selected from compound having sulfamate groups bonded to an aryl ring (specifically estrone sulfamates, p-(O-sulfamoyl)-N-alkanoyl-tyramines or coumarin sulfamates) and flavonoids or their derivatives.

Preferred Antigens: (II) are selected from natural or synthetic proteins, peptides, nucleic acids, altered peptide ligands, carbohydrates (including polysaccharides), lipopolysaccharides and antigens from biological resources (specifically bystander antigens); antigens associated with rheumatoid arthritis, multiple sclerosis, uveitis, type I diabetes, lupus erythematosus or infectious diseases; **heat-shock proteins**, proteolipids, myelin basic protein (MBP), myelin oligodendrocyte glycoprotein (MOG) or cell components of the uvea, skin, epithelium, thyroid, basal membrane, muscles, nerve cells, thymus or erythrocytes (of endogenous or other origin); or benzoyl penicillin, insulin, ovalbumin, lactalbumin or components of pollen, foods or house dust mites. (II) may be used in the form of a nucleic acid encoding the antigen.

Preferred Composition: (I) and (II) may be present separately. (A) may additionally contain auxiliaries, additives and/or adjuvants.

ABEX

UPTX: 20011024

SPECIFIC COMPOUNDS - Use of 25 compounds (I) is disclosed, e.g. estrone-3-O-sulfamate (Ia), p-O-sulfamoyl-N-tetradecanoyl-tyramine, 4-methyl-coumarin-7-O-sulfamate and dadzein-4'-O-sulfate.

ADMINISTRATION - Daily dose of (I) is 0.01-100 (preferably 1-10) mg/kg; and the weight ratio of (I) to (II) is 0.1-99.99 : 99.9-0.01 (preferably 10-90 : 90-10). (I) and (II) may be administered together or separately, e.g. by oral, intranasal, inhalation or parenteral routes.

L102 ANSWER 7 OF 10 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2001-281566 [29] WPIX

DNC C2001-085553

TI New amide compounds with antibacterial activity against Gram negative bacteria, and new fluorinated linker compounds useful in their

preparation.

DC B05 B06  
 IN FEX, T; HULTGREN, S J; KIHLEBERG, J; LARSSON, A; PINKNER, J; SVENSSON, A  
 PA (UNIW) UNIV WASHINGTON  
 CYC 94  
 PI WO 2001020995 A1 20010329 (200129)\* EN 85 A01N057-00  
 RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ  
 NL OA PT SD SE SL SZ TZ UG ZW  
 W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM  
 DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC  
 LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE  
 SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW  
 AU 2000078320 A 20010424 (200141) A01N057-00  
 ADT WO 2001020995 A1 WO 2000-US26177 20000922; AU 2000078320 A AU 2000-78320  
 20000922  
 FDT AU 2000078320 A Based on WO 2001020995  
 PRAI US 1999-155822P 19990923  
 IC ICM A01N057-00  
 ICS C07D305-00; C07D309-00; C07D311-00; C07D311-02; C07D311-04;  
 C07D321-00  
 AB WO 200120995 A UPAB: 20010528  
 NOVELTY - Amide derivatives (I) inhibit growth of Gram-negative bacteria  
 by inhibiting or preventing pilus biogenesis.  
 DETAILED DESCRIPTION - Amide derivatives of formula (I), and their  
 salts, esters or amines, are new:  
 R1, R2, R3 = 1-10C alkyl, 2-15C acyl, 6-14C aryl, heteroaryl, 7-15C  
 arylalkyl, heteroarylalkyl or heterocycloalkyl, each optionally  
 substituted;  
 R4 = CO2H, CONH2, -CHO, -B(OH)2, -PO(OH)2 or -COR; and  
 R = 13C alkyl optionally halo-substituted.  
 INDEPENDENT CLAIMS are included for the following:  
 (a) preparation and uses of (I);  
 (b) a new linker compound of formula (II):  
 (c) preparation of (II);  
 (d) a library of compounds (I);  
 (e) a method for monitoring solid-phase synthesis of (I) using a  
 linker compound attached to a solid support; and  
 (f) a complex comprising (I) complexed with a linker compound fixed  
 to a solid support.  
 R'1 = CO2H, -(CH2)nCO2H or O(CH2)nCO2H;  
 n = 1-10; and  
 R'2, R'3 = F or H, provided that when either R'2 or R'3 is F, then  
 the other is H.  
 ACTIVITY - Antibacterial.  
 MECHANISM OF ACTION - Pili assembly inhibitor.  
 (I) bind to a pilus **chaperone** (PapD **chaperone** or  
 FimC **chaperone**) inhibiting pili assembly. In a test to determine  
 inhibition of formation of the complex between PapD and PapG, % inhibition  
 of the complex between PapD and PapG at an inhibitor/PapD ratio of 38, was  
 31.5 % for N-benzyl-N-(2-oxo-2H-1-benzopyran-3-carbonyl) glycine.  
 USE - For treating, preventing or inhibiting bacterial infections  
 caused by Gram-negative organisms e.g. Escherichia coli, Haemophilus  
 influenzae, Salmonella enteritidis, Salmonella typhimurium, Bordetella  
 pertussis, Yersinia pestis, Yersinia enterocolitica, Helicobacter pylori  
 and Klebsiella pneumoniae, and preventing or inhibiting biofilm formation  
 or bacterial colonization by a Gram negative organism. (I) may be  
 administered alone or in combination with other antibiotics.  
 Dwg.0/4  
 FS CPI  
 FA AB; GI; DCN  
 MC CPI: B10-C04B; B10-D03; B11-C08; B12-K04A; B14-A01A  
 AB WO 200120995 A UPAB: 20010528  
 NOVELTY - Amide derivatives (I) inhibit growth of Gram-negative bacteria

by inhibiting or preventing pilus biogenesis.

DETAILED DESCRIPTION - Amide derivatives of formula (I), and their salts, esters or amines, are new:

R1, R2, R3 = 1-10C alkyl, 2-15C acyl, 6-14C aryl, heteroaryl, 7-15C arylalkyl, heteroarylalkyl or heterocycloalkyl, each optionally substituted;

R4 = CO<sub>2</sub>H, CONH<sub>2</sub>, -CHO, -B(OH)<sub>2</sub>, -PO(OH)<sub>2</sub> or -COR; and

R = 13C alkyl optionally halo-substituted.

INDEPENDENT CLAIMS are included for the following:

- (a) preparation and uses of (I);
- (b) a new linker compound of formula (II);
- (c) preparation of (II);
- (d) a library of compounds (I);
- (e) a method for monitoring solid-phase synthesis of (I) using a linker compound attached to a solid support; and
- (f) a complex comprising (I) complexed with a linker compound fixed to a solid support.

R'1 = CO<sub>2</sub>H, -(CH<sub>2</sub>)<sub>n</sub>CO<sub>2</sub>H or O(CH<sub>2</sub>)<sub>n</sub>CO<sub>2</sub>H;

n = 1-10; and

R'2, R'3 = F or H, provided that when either R'2 or R'3 is F, then the other is H.

ACTIVITY - Antibacterial.

MECHANISM OF ACTION - Pili assembly inhibitor.

(I) bind to a pilus **chaperone** (PapD **chaperone** or FimC **chaperone**) inhibiting pili assembly. In a test to determine inhibition of formation of the complex between PapD and PapG, % inhibition of the complex between PapD and PapG at an inhibitor/PapD ratio of 38, was 31.5 % for N-benzyl-N-(2-oxo-2H-1-benzopyran-3-carbonyl) glycine.

USE - For treating, preventing or inhibiting bacterial infections caused by Gram-negative organisms e.g. Escherichia coli, Haemophilus influenzae, Salmonella enteritidis, Salmonella typhimurium, Bordetella pertussis, Yersinia pestis, Yersinia enterocolitica, Helicobacter pylori and Klebsiella pneumoniae, and preventing or inhibiting biofilm formation or bacterial colonization by a Gram negative organism. (I) may be administered alone or in combination with other antibiotics.

Dwg.0/4

TECH

UPTX: 20010528

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation of Linker: Preparation of the linker compounds comprises:

- (a) hydrolyzing 1 of the ester moieties of dimethyl-2-fluoroterephthalate;
- (b) reducing the remaining ester; and
- (c) separating the 2 regioisomers.

Alternatively, the linker compounds are produced by:

- (a) dealkylating a 2-fluoro-4-propoxybenzoic acid;
- (b) reducing the carboxylic acid group to give a hydroxymethylphenol compound;
- (c) alkylating the phenolic hydroxyl group; and
- (d) hydrolyzing the product from (c) under basic conditions.

Preparation of (I): (I) can be prepared by:

- (1) condensing a compound of formula (III) with a salicylaldehyde, followed by cleavage from the solid support, to give a compound of formula (IA), i.e. (I) where R1 = H; R2 = (CH<sub>2</sub>)<sub>m</sub>A (m = 0-3; A = n-butyl, 2-methoxyethyl, benzyl or 2-(3-indolyl)-ethyl); R3 = **coumarin**;
- R4 = carboxyl; or

- (2) the following steps:

- (i) affixing a linker compound onto a solid support to give a benzylic alcohol;
- (ii) subjecting the benzylic alcohol to acylation with bromoacetic acid;
- (iii) subjecting the bromoacetate to a nucleophilic substitution with an amine;
- (iv) acylating with ethyl malonyl chloride to form an N-alkyl-N (malonamic acid ethyl ester)-glycine derivative;
- (v) condensing the product from (iv) with a salicylaldehyde; and

(vi) cleaving the compound from the linker compound under acidic or basic conditions.

Solid phase synthesis of (I) can be monitored by affixing the linker compound onto a solid support (e.g. polystyrene resin beads, silica chips and polyethylene glycol resins); measuring a signal from the linker compound and using the signal as an internal reference to monitor reactions. Typically the signal originating from the linker compound is a  $^{19}\text{F}$  resonance, which is measured by NMR spectroscopy.

ABEX

UPTX: 20010528

SPECIFIC COMPOUNDS - 8 Compounds (I) are specifically claimed, e.g. N-benzyl-N-(2-oxo-2H-1-benzopyran-3-carbonyl) glycine of formula (Ia); and N-(2-(1H-indol-3-yl)-ethyl)-N-(3-oxo-3H naphtho(2,1-b)pyran-2-carbonyl)-glycine. 4 Compounds (II) are specifically claimed, e.g. 3-fluoro-4-hydroxymethyl-phenoxy-acetic acid of formula (IIa):

ADMINISTRATION - Administration is by conventional routes.

Daily dosage is 1-1000 microg/kg.

EXAMPLE - N,N'-Diisopropylcarbodiimide (835 microl) was added to an ice-cold solution of pentafluorophenol (1.99 g) in EtOAc (30 ml). After 30 minutes, 3-fluoro-4-hydroxymethyl-phenoxyacetic acid (1.13 g) was added and the solution was stirred at 0 degrees C for 60 minutes. The mixture was added to resin (10 g), stirred for 12 hours at ambient temperature, washed and dried to give resin A.

DIC (1.04 ml) was added to a solution of bromoacetic acid (1.13 g) and 1-hydroxybenzotriazole (729 mg) in THF (30 ml), stirred and added to resin A (2.7 mmol, pre-swollen in THF), with N,N' dimethylaminopyridine (108 mg) in THF (10 ml). After stirring overnight, the resin was washed and dried. A solution of benzylamine (3 equivalents) in MeCN (30 ml) was added to the resin (2.7 mmol) at 0 degrees C, and after stirring for 90 minutes, the mixture was washed and dried.

Ethyl malonyl chloride (1.02 ml) in  $\text{CH}_2\text{Cl}_2$  (10 ml) was added to a suspension of the resin (2.7 mmol) and N,N'-diisopropylethylamine (1.38 ml) in  $\text{CH}_2\text{Cl}_2$  (20 ml) at 0 degrees C. After stirring for 60 minutes at 0 degrees C, the resin was washed and dried. A solution of salicylaldehyde (3 equivalents) in MeCN (7 ml) was added to the resin (pre-swollen in MeCN). The mixture was refluxed, and piperidine (1.2 equivalents) in MeCN (1 ml) added. After refluxing overnight, the resin was cooled, washed and dried.

Aqueous LiOH (1 M, 5 ml) was added to the resin (0.54 mmol) in THF/ $\text{H}_2\text{O}$ /MeOH (3:1:1, 40 ml) at 0 degrees C. After 2.5 hours at ambient temperature, the resin was filtered off. The filtrate concentrated almost to dryness, then concentrated from toluene. The residue was dissolved in a mixture of EtOAc (30 ml) and aqueous HCl (0.05 M, 10 ml). The organic phase was worked up and flash column chromatography gave N-benzyl-N-(2-oxo-2H-1 benzopyran-3-carbonyl)-glycine (44 %).

L102 ANSWER 8 OF 10 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2000-572228 [53] WPIX

DNC C2000-170660

TI Method of inhibiting binding of a **chaperone** protein, with its client protein or client polypeptide, using a **coumarin** or a **coumarin** derivative.

DC B02

IN MARCU, M G; NECKERS, L M; SCHULTE, T W

PA (USSH) US DEPT HEALTH &amp; HUMAN SERVICES

CYC 92

PI WO 2000053169 A2 20000914 (200053)\* EN 20 A61K031-00

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL  
OA PT SD SE SL SZ TZ UG ZW

W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE  
ES FI GB GD GE GH GR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR  
LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK  
SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2000037406 A 20000928 (200067)  
 EP 1161231 A2 20011212 (200204) EN A61K031-00  
 R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT  
 RO SE SI

JP 2003523313 W 20030805 (200353) 30 A61K031-353  
 ADT WO 2000053169 A2 WO 2000-US6482 20000310; AU 2000037406 A AU 2000-37406  
 20000310; EP 1161231 A2 EP 2000-916277 20000310, WO 2000-US6482 20000310;  
 JP 2003523313 W JP 2000-603658 20000310, WO 2000-US6482 20000310  
 FDT AU 2000037406 A Based on WO 2000053169; EP 1161231 A2 Based on WO  
 2000053169; JP 2003523313 W Based on WO 2000053169  
 PRAI US 1999-124135P 19990312  
 IC ICM A61K031-00; A61K031-353  
 ICS A61K031-7048; A61K031-7052; A61P031-20; A61P035-00; A61P043-00;  
 C07D311-10; C07D311-46; C07D311-56; C07H017-075; C12N009-99  
 AB WO 200053169 A UPAB: 20001023

NOVELTY - A method of inhibiting binding of a **chaperone** protein,  
 with its client protein or client polypeptide, using a **coumarin**  
 or a **coumarin** derivative.

DETAILED DESCRIPTION - A method of inhibiting binding of a  
**chaperone** protein with its client protein or client polypeptide.  
 The **chaperone** protein is contacted with a **coumarin** or  
 a **coumarin** derivative, such that the **coumarin** or the  
**coumarin** derivative binds the **chaperone** protein, which  
 inhibits the **chaperone** protein from binding its client protein  
 or client polypeptide. The client protein or the client polypeptide is  
 inactive or less active subsequent to binding of the **chaperone**  
 protein to **coumarin** or the **coumarin** derivative.

ACTIVITY - Cytostatic.

MECHANISM OF ACTION - **Chaperone** protein antagonist.

To demonstrate binding of a **chaperone** protein to  
**novobiocin**, the **novobiocin** was first immobilized on  
 sepharose. A **chaperone** protein, either pure **Hsp90**, or  
 a solution containing **Hsp90** in a cell lysate, was subsequently  
 incubated with the immobilized **novobiocin**. The cell lysate was  
 preincubated with various members of the **coumarin** family of  
 antibiotics, namely **novobiocin**, **chlorobiocin** or  
**coumermycin A1** and also ATP to determine their ability to inhibit  
 binding of the **Hsp90**. The amount of **Hsp90** bound to the  
 immobilized **novobiocin** was analyzed. Immobilized  
**novobiocin** bound in a hydrophobic manner to both of the pure  
**Hsp90** and the **Hsp90** present in cell lysate.  
 Pre-incubation of the cell lysate with excess soluble **novobiocin**  
 , **chlorobiocin**, **coumermycin A1**, or ATP inhibited, in a  
 dose-dependent manner, subsequent **Hsp90** binding to immobilized  
**novobiocin**. Soluble **novobiocin** inhibited **Hsp90**  
 binding to immobilized **novobiocin** at 8 mM. **Chlorobiocin**  
 and **coumermycin A1** inhibited **Hsp90** binding to  
 immobilized **novobiocin** at 0.5 mM, while ATP inhibited  
**Hsp90** binding between 10 and 15 mM, as demonstrated by silver  
 staining.

These data demonstrate that **novobiocin** binds to  
**chaperone** proteins such as **Hsp90** and that subsequent  
**Hsp90**-binding can be inhibited by contact with the  
**coumarin** derivatives.

USE - Used as **chaperone** protein antagonist.

**Chaperone** proteins interact with a variety of proteins involved in  
 cell proliferation. One such **chaperone** protein, **heat**  
**shock protein (Hsp)90** is expressed  
 at 2-10 fold higher levels in tumor cells compared to their normal  
 counterparts (see Ferrarini et al., Int. J. Cancer 51:613-619 (1992)).  
 Method can be used to interfere with the **chaperone** protein  
 function of **Hsp90**. The **coumarin** or a **coumarin**  
 derivative can be used to bind **Hsp90** and to interfere with its

function, including its function in tumor cell proliferation.

**ADVANTAGE** - Present method better suited in clinical applications compared to the use of other compounds of prior art which display in vivo toxicity unrelated to their **Hsp90** antagonism.

Dwg.0/0

FS CPI

FA AB; DCN

MC CPI: B02-C01; B02-N; B06-A01; B14-H01B; B14-L06

AB WO 200053169 A UPAB: 20001023

**NOVELTY** - A method of inhibiting binding of a **chaperone** protein, with its client protein or client polypeptide, using a **coumarin** or a **coumarin** derivative.

**DETAILED DESCRIPTION** - A method of inhibiting binding of a **chaperone** protein with its client protein or client polypeptide. The **chaperone** protein is contacted with a **coumarin** or a **coumarin** derivative, such that the **coumarin** or the **coumarin** derivative binds the **chaperone** protein, which inhibits the **chaperone** protein from binding its client protein or client polypeptide. The client protein or the client polypeptide is inactive or less active subsequent to binding of the **chaperone** protein to **coumarin** or the **coumarin** derivative.

**ACTIVITY** - Cytostatic.

**MECHANISM OF ACTION** - **Chaperone** protein antagonist.

To demonstrate binding of a **chaperone** protein to **novobiocin**, the **novobiocin** was first immobilized on sepharose. A **chaperone** protein, either pure **Hsp90**, or a solution containing **Hsp90** in a cell lysate, was subsequently incubated with the immobilized **novobiocin**. The cell lysate was preincubated with various members of the **coumarin** family of antibiotics, namely **novobiocin**, **chlorobiocin** or **coumermycin A1** and also ATP to determine their ability to inhibit binding of the **Hsp90**. The amount of **Hsp90** bound to the immobilized **novobiocin** was analyzed. Immobilized **novobiocin** bound in a hydrophobic manner to both of the pure **Hsp90** and the **Hsp90** present in cell lysate. Pre-incubation of the cell lysate with excess soluble **novobiocin**, **chlorobiocin**, **coumermycin A1**, or ATP inhibited, in a dose-dependent manner, subsequent **Hsp90** binding to immobilized **novobiocin**. Soluble **novobiocin** inhibited **Hsp90** binding to immobilized **novobiocin** at 8 mM. **Chlorobiocin** and **coumermycin A1** inhibited **Hsp90** binding to immobilized **novobiocin** at 0.5 mM, while ATP inhibited **Hsp90** binding between 10 and 15 mM, as demonstrated by silver staining.

These data demonstrate that **novobiocin** binds to **chaperone** proteins such as **Hsp90** and that subsequent **Hsp90**-binding can be inhibited by contact with the **coumarin** derivatives.

**USE** - Used as **chaperone** protein antagonist.

**Chaperone** proteins interact with a variety of proteins involved in cell proliferation. One such **chaperone** protein, **heat shock protein (Hsp)90** is expressed at 2-10 fold higher levels in tumor cells compared to their normal counterparts (see Ferrarini et al., Int. J. Cancer 51:613-619 (1992)). Method can be used to interfere with the **chaperone** protein function of **Hsp90**. The **coumarin** or a **coumarin** derivative can be used to bind **Hsp90** and to interfere with its function, including its function in tumor cell proliferation.

**ADVANTAGE** - Present method better suited in clinical applications compared to the use of other compounds of prior art which display in vivo toxicity unrelated to their **Hsp90** antagonism.

Dwg.0/0

TECH

UPTX: 20001023

TECHNOLOGY FOCUS - PHARMACEUTICALS - The interaction between the **chaperone** protein and **coumarin** or **coumarin** derivative is such that the **chaperone** protein does not bind or binds with less affinity to its client protein or client polypeptide. Such interference with binding can be accomplished by any suitable method. Preferably the **chaperone** protein is **Hsp90** and the **coumarin** or **coumarin** derivative is **novobiocin** and the interaction is such that **novobiocin** binds a carboxy-terminal region of **Hsp90**, which contains an adenosine triphosphate (ATP)-binding domain.

ABEX. UPTX: 20001023

SPECIFIC COMPOUNDS - The **coumarin** or **coumarin** derivative is preferably a **coumarin** antibiotic. The **coumarin** antibiotic is **chlorobiocin** or **coumermycin A1** or preferably **novobiocin**. The client protein or the client polypeptide is a tyrosine or serine/threonine kinase. The client protein or the client polypeptide is tyrosine kinase p185erbB2 or p60v-src, serine/threonine kinase Raf-1 or a mutated p53 protein.

L102 ANSWER 9 OF 10 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2000-364887 [31] WPIX

DNC C2000-110106

TI Dry-cleaning system for dry-cleaning of fabrics comprises dry-cleaning composition.

DC A25 A26 A97 D25 E19

IN SMITH, J A

PA (CUST-N) CUSTOM CLEANER INC; (HENK) HENKEL KGAA

CYC 83

PI WO 2000023647 A1 20000427 (200031)\* EN 53 D06L001-12

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL  
OA PT SD SE SZ UG ZW

W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD  
GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD  
MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA  
UG US UZ VN YU ZW

AU 9911096 A 20000508 (200037) D06L001-12

ADT WO 2000023647 A1 WO 1998-US22243 19981022; AU 9911096 A WO 1998-US22243 19981022, AU 1999-11096 19981022

FDT AU 9911096 A Based on WO 2000023647

PRAI WO 1998-US22243 19981022

IC ICM D06L001-12

ICS C11D003-37; C11D017-04; D06L001-04

AB WO 200023647 A UPAB: 20000630

NOVELTY - A dry-cleaning system for the dry-cleaning or fabric-freshening of a fabric article comprises a dry-cleaning composition which contains polysulfonic acid and water.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following: (A) cleaning or freshening of a soiled fabric article (2) with (1) which comprises: (a) placing (2) and (1) into a bag which includes an opening. The opening comprises a fastening system so that the bags can enclose (2) in a vapor impermeable manner, (b) closing the system to form the bag into a closed system which comprises (2) and (1), (c) tumbling the closed system in a rotary clothes dryer at an elevated temperature, so that (1) contacts (2) to disperse the soil, and (d) opening the fastening system and removing the cleaned or freshened fabric article from the bag; (B) removing a stain from a soiled fabric article comprises steps (a), (b), (c) and (d); (C) a kit for dry cleaning or fabric freshening a fabric article comprises (1) and a bag.

USE - In dry-cleaning or fabric freshening of all fabrics, including wool, leather, nylon, cotton, polyester etc. as well as delicate fabrics such as 100% acetate, silk, rayon and blends of these fabrics.

ADVANTAGE - (1) does not include solvents like perchloroethylene or

other undesirable hydrocarbon solvents. (1) removes stains and improves the slip characteristics to fabrics (e.g. reduction in drag).

Dwg.0/0

FS

CPI

FA

AB; DCN

MC

CPI: A12-W12A; D11-B19; E06-A01; E06-D01; E07-A02C; E07-A03C; E10-B02A; E10-D01D; E10-E02F1; E10-E04H; E10-E04J; E10-E04L4; E10-E04L5; E10-E04M3; E10-E04M4; E10-F02; E10-G02F1; E10-G02H2; E10-H01E

AB

WO 200023647 A UPAB: 20000630

NOVELTY - A dry-cleaning system for the dry-cleaning or fabric-freshening of a fabric article comprises a dry-cleaning composition which contains polysulfonic acid and water.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following: (A) cleaning or freshening of a soiled fabric article (2) with (1) which comprises: (a) placing (2) and (1) into a bag which includes an opening. The opening comprises a fastening system so that the bags can enclose (2) in a vapor impermeable manner, (b) closing the system to form the bag into a closed system which comprises (2) and (1), (c) tumbling the closed system in a rotary clothes dryer at an elevated temperature, so that (1) contacts (2) to disperse the soil, and (d) opening the fastening system and removing the cleaned or freshened fabric article from the bag; (B) removing a stain from a soiled fabric article comprises steps (a), (b), (c) and (d); (C) a kit for dry cleaning or fabric freshening a fabric article comprises (1) and a bag.

USE - In dry-cleaning or fabric freshening of all fabrics, including wool, leather, nylon, cotton, polyester etc. as well as delicate fabrics such as 100% acetate, silk, rayon and blends of these fabrics.

ADVANTAGE - (1) does not include solvents like perchloroethylene or other undesirable hydrocarbon solvents. (1) removes stains and improves the slip characteristics to fabrics (e.g. reduction in drag).

Dwg.0/0

TECH

UPTX: 20000630

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Composition: (1) comprises (wt.%): polysulfonic acid (about 0.25 - 20) and water (about 10 - 99.75). (1) additionally comprises (wt.%): at least 1 water-miscible or partially water-miscible organic solvent (about 1 - 85), surfactants (about 0.01 - 10), gelling agents or viscosity modifiers and a compound (about 0.2 - 5) or the organic solvent is selected from glycol ethers (preferably dipropylene glycol n-propyl ether, dipropylene glycol n-butyl ether or tripropylene glycol methyl ether), 3-methoxy-3-methyl-1-butanol, liquid polyethylene glycols, 2 - 4C polyols and/or lactones (approximately g-butyro-lactone): (1) further comprises an agent selected from fabric-softening agents, anti-creasing agents, anti-soil agents, bacteriostatic agents, brightening agents, bodying agents, dyes fiber emollients, finishing agents, fragrances, germicides, lubricants, mildew-proofing agents, moth-proofing agents, shrinkage controllers and/or sizing agents. The compound which has vapor tension of at most 4 Pa at 25degreesC, is selected from 10 - 12C aliphatic alcohols, 10 - 13C aldehydes, 13 - 18C aliphatic ketones, aromatic ketones (up to 18C) having a musk odor, 8 - 15C aliphatic esters, methyl anthranilate, methyl N-methylantranilate, p-cresyl phenylacetate, amyl salicylate, coumarin, dihydrocoumarin, gammadecalactone, dodecalactone, undecalactone, eugenol, isoeugenol, diphenyl oxide, the methyl and ethyl ethers of naphthol, galaxolide, indole and its reaction products with hydroxycitronella, tridecene-2-nitrile, and 2-(2'-methyl-pent-2'-enyl)-5-methyl pyridine. (1) is present in a spray or roll on solution, on a substrate. The substrate is selected from sheet, sponge, dauber, stick, granules or cube (preferably sheet). The bag has an interior surface, at least a portion of which has (1) releasably absorbed. The bag is formed of a flexible non-porous material which is not damaged upon exposure to agitation and to a temperature to cause the release of (1) from the surface. Preferred Method: The amount of (1) prior to step (a) is applied by rubbing, dabbing, spraying, rolling on or dipping (2)



with (1) so as to loosen and remove stain from (2).

ABEX

UPTX: 20000630

EXAMPLE - The dry-cleaning composition were prepared by adding polysulfonic acid (HSP-1180) (i) and distilled water to a vessel with a stirrer. The solvent(s) and remaining materials such as surfactants, fragrances etc. were added individually with agitation. The system pH was adjusted after the acid is added or at the end of preparation. Two formulations of the composition were prepared. First formulation (I) comprises (%): Arcolsolv (RTM; DPNB is dipropylene glycol n-propyl ether) (ii) (42.03), Arcolsolv TPM (iii) (50.95), distilled water (iv) (2.90), Tergitol (RTM; 15 - S - 3 is a nonionic surfactant) (v) (0.41), Igepal (RTM; CO-660 is a nonionic surfactant) (vi) (0.58), (i) (2.90) and Frag DC1212 (fragrance) (vii) (0.23). second formulation (II) comprises (%): Arcolsolv (RTM; DPNP is dipropylene glycol t-butyl ether) (55.96), (iii) (15.94), (iv) (25.00), (v) (0.80), (vi) (1.00), (i) (1.00) and (vii) (0.50). The formulations were tested in a stain removal procedure. Stains including spaghetti and gravy were placed on fabric, left to dry for 24 - 48 hours and gently scraped to remove the excess stain. A clean paper towel was placed under the stain on the cloth swatch. Then the cloth swatch was subjected to 10 seconds rubbing with paper towel, moved to a clean spot on the paper towel, subjected to 20 seconds further rubbing (2 times) and again moved to a clean spot on the paper. The cloth swatch was put aside to air dry. All cloth swatches were taken from fabrics supplied by Test fabrics. The fabric type for (I) was 100% worsted flannel and the stain type was Estee Lauder lipstick. The % stain removal was 100 which means no visual sign of the original stain remained on the fabric. The fabric type for (II) was span viscose challis and the stain type was Wishbone Deluxe French dressing. The % stain removal was 90.

L102 ANSWER 10 OF 10 WPIX COPYRIGHT 2004 THOMSON DERWENT on STN

AN 2000-237778 [20] WPIX

DNC C2000-072438

TI Vaccinating mammals by administering, appropriate vector, nucleotide sequence encoding antigenic peptide and compound enhancing humoral and cellular immune responses initiated by peptide.

DC B05

IN CHARO, J; KIESSLING, R

PA (GLAX) GLAXO GROUP LTD

CYC 89

PI WO 2000012121 A1 20000309 (200020)\* EN 65 A61K039-00

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL

OA PT SD SE SL SZ UG ZW

W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES

FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS

LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ

TM TR TT UA UG US UZ VN YU ZA ZW

AU 9957402 A 20000321 (200031) A61K039-00

NO 2001000922 A 20010423 (200130) A61K000-00

EP 1107785 A1 20010620 (200135) EN A61K039-00

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT

RO SE SI

CZ 2001000717 A3 20011017 (200172) A61K039-00

BR 9913323 A 20011204 (200203) A61K039-00

KR 2001072983 A 20010731 (200209) A61K048-00

HU 2001003214 A2 20011228 (200216) A61K039-00

CN 1326358 A 20011212 (200225) A61K039-00

ZA 2001001539 A 20020424 (200237) 74 A61K000-00

AU 747643 B 20020516 (200244) A61K039-00

JP 2002523469 W 20020730 (200264) 73 A61K039-00

MX 2001002043 A1 20011101 (200279) A61K039-00

NZ 510206 A 20030829 (200365) A61K039-00

ADT WO 2000012121 A1 WO 1999-EP6217 19990825; AU 9957402 A AU 1999-57402

19990825; NO 2001000922 A WO 1999-EP6217 19990825, NO 2001-922 20010223; EP 1107785 A1 EP 1999-944505 19990825, WO 1999-EP6217 19990825; CZ 2001000717 A3 WO 1999-EP6217 19990825, CZ 2001-717 19990825; BR 9913323 A BR 1999-13323 19990825, WO 1999-EP6217 19990825; KR 2001072983 A KR 2001-702431 20010226; HU 2001003214 A2 WO 1999-EP6217 19990825, HU 2001-3214 19990825; CN 1326358 A CN 1999-812463 19990825; ZA 2001001539 A ZA 2001-1539 20010223; AU 747643 B AU 1999-57402 19990825; JP 2002523469 W WO 1999-EP6217 19990825, JP 2000-567235 19990825; MX 2001002043 A1 MX 2001-2043 20010226; NZ 510206 A NZ 1999-510206 19990825, WO 1999-EP6217 19990825

FDT AU 9957402 A Based on WO 2000012121; EP 1107785 A1 Based on WO 2000012121; CZ 2001000717 A3 Based on WO 2000012121; BR 9913323 A Based on WO 2000012121; HU 2001003214 A2 Based on WO 2000012121; AU 747643 B Previous Publ. AU 9957402, Based on WO 2000012121; JP 2002523469 W Based on WO 2000012121; NZ 510206 A Based on WO 2000012121

PRAI GB 1998-18627 19980826

IC ICM A61K000-00; A61K039-00; A61K048-00

ICS A61K039-39; A61P031-00; A61P031-12; A61P037-00; A61P037-04

AB WO 200012121 A UPAB: 20021105

NOVELTY - A method of vaccinating mammals against disease states by administering to the mammal, with an appropriate vector, a nucleotide sequence encoding an antigenic peptide associated with the disease state and additionally administering a compound that enhances both humoral and cellular immune responses initiated by the antigenic peptide.

DETAILED DESCRIPTION - The compound is 4-(2-formyl-3-hydroxyphenoxy)methylbenzoic acid, 5-(2-formyl-3-hydroxyphenoxy)pentanamide, N,N-diethyl-5-(2-formyl-3-hydroxyphenoxy)pentanamide, N-isopropyl-5-(2-formyl-3-hydroxyphenoxy)pentanamide, ethyl 5-(2-formyl-3-hydroxyphenoxy)pentanoate, 5-(2-formyl-3-hydroxyphenoxy)pentanonitrile, ( plus or minus )-5-(2-formyl-3-hydroxyphenoxy)-2-dimethylpentanoic acid, 5-(2-formyl-3-hydroxyphenoxy)-2,2-dimethylpentanoic acid, methyl 3-(2-formyl-3-hydroxyphenoxy)methylbenzoate, 3-(2-formyl-3-hydroxyphenoxy)methylbenzoic acid, benzyl 5-(2-formyl-3-hydroxyphenoxy)pentanoate, 5-(4-(2-formyl-3-hydroxyphenoxy)-N-butyl)tetrazole, 7-(2-formyl-3-hydroxyphenoxy)heptanoic acid, 5-(2-formyl-3-hydroxyphenoxy-4-n-propoxyphenoxy)pentanoic acid, 5-(4,6-dichloro-2-formyl-3-hydroxyphenoxy)pentanoic acid, 5-(2-formyl-3-hydroxyphenoxy)-N-methylsulfonylpentanamide, ethyl 4-(2-formyl-3-hydroxyphenoxy)methylbenzoate, 5-(4-chloro-2-formyl-3-hydroxyphenoxy)pentanoic acid, 5-(3-acetylamino-2-formylphenoxy)pentanoic acid, aminoguanidine, 4-(2-formyl-3-hydroxyphenoxy)butanoic acid, 6-(2-formyl-3-hydroxyphenoxy)hexanoic acid, ethyl 4-(3-acetylamino-2-formylphenoxy)methylbenzoate, 4-(3-acetylamino-2-formylphenoxy)methylbenzoic acid, 2-(2-formyl-3-hydroxyphenoxy)methylbenzoic acid, 5-(4-(2-formyl-3-hydroxyphenoxy)methyl)phenyltetrazole, 5-(2-formyl-3-hydroxy-4-methoxyphenoxy)pentanoic acid, 3-(2-formyl-3-hydroxyphenoxy)propionitrile, 4-hydroxyphenylacetaldehyde, 1-hydroxy-2-phenylpropane, 3-phenylpropanaldehyde, 4-nitrobenzaldehyde, methyl 4-formylbenzoate, 4-chlorobenzaldehyde, 4-methoxybenzaldehyde, 4-methylbenzaldehyde, 8,10-dioxoundecanoic acid, 4,6-dioxoheptanoic acid, pentanedione, 5-methoxy-1-tetralone, 6-methoxy-1-tetralone, 7-methoxy-1-tetralone, 2-tetralone, 3-hydroxy-1-(4-methoxyphenyl)-3-methyl-2-butanone, 2',4'-dihydroxy-2-(4-methoxyphenyl)acetophenone, 2-hydroxy-1-(4-methoxyphenyl)-pent-2-en-4-one, naringenin 4',5,6-trihydroxyflavonone, 4'-methoxy-2-(4-methoxyphenyl)acetophenone, 6,7-dihydroxycoumarin, 7-methoxy-2-tetralone, 6,7-dimethoxy-2-tetralone, 6-hydroxy-4-methylcoumarin, homogentisic acid gamma lactone, 6-hydroxy-1,2-naphthoquinone or 8-methoxy-2-tetralone and their physiologically acceptable salts.

ACTIVITY - Immunostimulant; antiviral; antibacterial; antiparasitic; anticancer; antiallergic; immunomodulatory.

MECHANISM OF ACTION - None given.

USE - The methods are used to vaccinate mammals against disease states (claimed). They are used to protect mammals against a variety of disease states such as viral, bacterial or parasitic infections caused by hepatitis viruses A, B, C, D and E, HIV, herpes viruses 1, 2, 6 and 7, cytomegalovirus, varicella zoster, papilloma virus, Epstein-Barr virus, influenza viruses, para-influenza viruses, adenoviruses, coxsackie viruses, picornaviruses, rotaviruses, respiratory syncytial viruses, pox viruses, rhinoviruses, rubella virus, papovirus, mumps virus, measles virus, mycobacteria causing tuberculosis and leprosy, pneumococci, aerobic Gram-negative bacilli, mycoplasma, staphylococci, streptococci, salmonellae, chlamydiae and including malaria, leishmaniasis, trypanosomiasis, toxoplasmosis, schistosomiasis and filariasis, cancers such as breast, colon, rectal, head and neck, renal, laryngeal, ovarian, cervical and prostate cancers, and malignant melanomas, allergies such as rhinitis due to house dust mite, pollen or other environmental allergens, and autoimmune diseases including systemic lupus erythematosus.

ADVANTAGE - The method shows the dual action of stimulating humoral immune response while simultaneously stimulating the cellular immune response mechanism, to raise both serum antibody levels and cytokine T lymphocyte levels. Immunization with a plasmid DNA coding for mycobacterial **heat shock protein** (M.hsp65) antigen was compared between for control plasmid (p3), p3 plus tucarecol (1 mg), p3M.65, p3M.65 plus tucarecol, plasmid expressing granulocyte-macrophage colony-stimulating factor (p3M.65 G) and plasmid expressing gamma interferon (p3M.65I). Significant amounts of antibodies to M.hsp65 could be detected in sera from p3M.65-immunized mice, but not in p3 immunized mice. Antibody titers were increased markedly when tucarecol was administered subcutaneously simultaneously with the M.hsp plasmid (p3M.65, T). In contrast, no increase in specific antibody response was detected in mice immunized with control plasmid and tucarecol excluding the possibility that a general increase in non-specific cross-reactive antibodies due to the high degree of immuno-potential associated with tucarecol administration accounted for the observed effect.

DESCRIPTION OF DRAWING(S) - Effects of tucarecol on the specific antibody response to mycobacterial hsp65 after immunization with pDNA expressing M.hsp65.

Dwg.3A/9

FS CPI  
FA AB; GI; DCN  
MC CPI: B04-E02F; B04-E03F; B06-A01; B07-A02A; B07-A03; B07-D07; B07-D13; B10-B02; B10-C03; B10-C04; B10-D01; B10-E02; B10-F02; B10-G02; B14-A01; B14-A02; B14-B02; B14-G01; B14-G02A; B14-G03; B14-H01; B14-S11

AB WO 200012121 A UPAB: 20021105

NOVELTY - A method of vaccinating mammals against disease states by administering to the mammal, with an appropriate vector, a nucleotide sequence encoding an antigenic peptide associated with the disease state and additionally administering a compound that enhances both humoral and cellular immune responses initiated by the antigenic peptide.

DETAILED DESCRIPTION - The compound is 4-(2-formyl-3-hydroxyphenoxy)methylbenzoic acid, 5-(2-formyl-3-hydroxyphenoxy)pentanamide, N,N-diethyl-5-(2-formyl-3-hydroxyphenoxy)pentanamide, N-isopropyl-5-(2-formyl-3-hydroxyphenoxy)pentanamide, ethyl 5-(2-formyl-3-hydroxyphenoxy)pentanoate, 5-(2-formyl-3-hydroxyphenoxy)pentanonitrile, ( plus or minus )-5-(2-formyl-3-hydroxyphenoxy)-2- dimethylpentanoic acid, 5-(2-formyl-3-hydroxyphenoxy)-2,2-dimethylpentanoic acid, methyl 3-(2-formyl-3-hydroxyphenoxy)methylbenzoate, 3-(2-formyl-3-hydroxyphenoxy)methylbenzoic acid, benzyl 5-(2-formyl-3-hydroxyphenoxy)pentanoate, 5-(4-(2-formyl-3-hydroxyphenoxy)-N-butyl)tetrazole, 7-(2-formyl-3-hydroxyphenoxy)heptanoic acid,

5-(2-formyl-3-hydroxyphenoxy-4-n-propoxyphenoxy)pentanoic acid,  
 5-(4,6-dichloro-2-formyl-3-hydroxyphenoxy)pentanoic acid,  
 5-(2-formyl-3-hydroxyphenoxy)-N-methylsulfonylpentanamide, ethyl  
 4-(2-formyl-3-hydroxyphenoxy)methyl)benzoate, 5-(4-chloro-2-formyl-3-hydroxyphenoxy)pentanoic acid, 5-(3-acetylamino-2-formylphenoxy)pentanoic acid, aminoguanidine, 4-(2-formyl-3-hydroxyphenoxy)butanoic acid, 6-(2-formyl-3-hydroxyphenoxy)hexanoic acid, ethyl 4-(3-acetylamino-2-formylphenoxy)methyl)benzoate, 4-(3-acetylamino-2-formylphenoxy)methyl)benzoic acid, 2-(2-formyl-3-hydroxyphenoxy)methyl)benzoic acid, 5-(4-(2-formyl-3-hydroxyphenoxy)methyl)phenyl)tetrazole, 5-(2-formyl-3-hydroxy-4-methoxyphenoxy)pentanoic acid, 3-(2-formyl-3-hydroxyphenoxy)propionitrile, 4-hydroxyphenylacetaldehyde, 1-hydroxy-2-phenylpropane, 3-phenylpropanaldehyde, 4-nitrobenzaldehyde, methyl 4-formylbenzoate, 4-chlorobenzaldehyde, 4-methoxybenzaldehyde, 4-methylbenzaldehyde, 8,10-dioxoundecanoic acid, 4,6-dioxoheptanoic acid, pentanedione, 5-methoxy-1-tetralone, 6-methoxy-1-tetralone, 7-methoxy-1-tetralone, 2-tetralone, 3-hydroxy-1-(4-methoxyphenyl)-3-methyl-2-butanone, 2',4'-dihydroxy-2-(4-methoxyphenyl)acetophenone, 2-hydroxy-1-(4-methoxyphenyl)-pent-2-en-4-one, naringenin 4',5,6-trihydroxyflavonone, 4'-methoxy-2-(4-methoxyphenyl)acetophenone, 6,7-dihydroxycoumarin, 7-methoxy-2-tetralone, 6,7-dimethoxy-2-tetralone, 6-hydroxy-4-methylcoumarin, homogentisic acid gamma lactone, 6-hydroxy-1,2-naphthoquinone or 8-methoxy-2-tetralone and their physiologically acceptable salts.

ACTIVITY - Immunostimulant; antiviral; antibacterial; antiparasitic; anticancer; antiallergic; immunomodulatory.

MECHANISM OF ACTION - None given.

USE - The methods are used to vaccinate mammals against disease states (claimed). They are used to protect mammals against a variety of disease states such as viral, bacterial or parasitic infections caused by hepatitis viruses A, B, C, D and E, HIV, herpes viruses 1, 2, 6 and 7, cytomegalovirus, varicella zoster, papilloma virus, Epstein-Barr virus, influenza viruses, para-influenza viruses, adenoviruses, coxsackie viruses, picornaviruses, rotaviruses, respiratory syncytial viruses, pox viruses, rhinoviruses, rubella virus, papovirus, mumps virus, measles virus, mycobacteria causing tuberculosis and leprosy, pneumococci, aerobic Gram-negative bacilli, mycoplasma, staphylococci, streptococci, salmonellae, chlamydiae and including malaria, leishmaniasis, trypanosomiasis, toxoplasmosis, schistosomiasis and filariasis, cancers such as breast, colon, rectal, head and neck, renal, laryngeal, ovarian, cervical and prostate cancers, and malignant melanomas, allergies such as rhinitis due to house dust mite, pollen or other environmental allergens, and autoimmune diseases including systemic lupus erythematosus.

ADVANTAGE - The method shows the dual action of stimulating humoral immune response while simultaneously stimulating the cellular immune response mechanism, to raise both serum antibody levels and cytokine T lymphocyte levels. Immunization with a plasmid DNA coding for mycobacterial heat shock protein (M.hsp65) antigen was compared between for control plasmid (p3), p3 plus tucaresol (1 mg), p3M.65, p3M.65 plus tucaresol, plasmid expressing granulocyte-macrophage colony-stimulating factor (p3M.65 G) and plasmid expressing gamma interferon (p3M.65I). Significant amounts of antibodies to M.hsp65 could be detected in sera from p3M.65-immunized mice, but not in p3 immunized mice. Antibody titers were increased markedly when tucaresol was administered subcutaneously simultaneously with the M.hsp plasmid (p3M.65, T). In contrast, no increase in specific antibody response was detected in mice immunized with control plasmid and tucaresol excluding the possibility that a general increase in non-specific cross-reactive antibodies due to the high degree of immuno-potentiation associated with tucaresol administration accounted for the observed effect.

DESCRIPTION OF DRAWING(S) - Effects of tucaresol on the specific

antibody response to mycobacterial hsp65 after immunization with pDNA expressing M.hsp65.

Dwg.3A/9

TECH

UPTX: 20000426

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Method - Administration of the compound takes place on 1-7 occasions, between 14 (7; 24) days prior to and 14 (7; 24) days after administration of the nucleotide sequence. Administration of the compound is substantially simultaneous with administration of the nucleotide sequence. Administration is repeated 1-4 times at intervals of 1 day-18 months and is oral, nasal, pulmonary, intramuscular, subcutaneous, intradermal or topical, preferably by a gene-gun delivery technique. The compound is administered at a dose of 0.1-100 mg/kg/administration. The mammal is human. Preferred Compound - The compound is 4-(2-formyl-3-hydroxyphenoxymethyl)benzoic acid.

ABEX

UPTX: 20000426

ADMINISTRATION - Administration of the compound takes place on 1-7 occasions, between 14 (7; 24) days prior to and 14 (7; 24) days after administration of the nucleotide sequence (claimed). Administration of the compound is substantially simultaneous with administration of the nucleotide sequence (claimed). Administration is repeated 1-4 times at intervals of 1 day-18 months (claimed). Administration is oral, nasal, pulmonary, intramuscular, subcutaneous, intradermal or topical, preferably by a gene-gun delivery technique (claimed). The compound is administered at a dose of 0.1-100 mg/kg/administration (claimed) preferably 0.1-10 (1-5) mg/kg/administration. The mammals are human (claimed) as well as domestic animals, laboratory animals, farm animals and captive wild animals. Administration is separate, sequential or concomitant (claimed).

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